Actelion receives US FDA approval of Uptravi (selexipag) for the treatment of pulmonary arterial hypertension

- Uptravi® approved for treatment of pulmonary arterial hypertension (PAH, WHO Group 1) to delay disease progression and reduce the risk of hospitalization for PAH
- Uptravi will be made available to patients in the US in early January 2016
- Uptravi will become a significant treatment option in PAH and complements Actelion’s portfolio with Opsumit® and Veletri®

ALLSCHWIL, SWITZERLAND – 22 December 2015 – Actelion (SIX: ATLN) announced today that the United States Food and Drug Administration (FDA) has approved the use of the orally active, selective IP prostacyclin receptor agonist Uptravi (selexipag), originally discovered and synthesized by Nippon Shinyaku, for the treatment of pulmonary arterial hypertension (PAH).

Uptravi is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms. Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), PAH associated with congenital heart disease with repaired shunts (10%).

Vallerie McLaughlin MD, Director of the Pulmonary Hypertension Program in the Division of Cardiovascular Medicine at the University of Michigan, United States, commented: “The prostacyclin pathway has long been recognized as a key target in PAH treatment. However, until now, it has been underutilized. This is in part due to the significant burden existing prostanoid treatments have placed on the patients and on those supporting them. The approval of Uptravi with its convincing long-term outcome results means that many more patients can benefit from this pathway and be treated much earlier in the course of their disease.”

Jean-Paul Clozel, MD and Chief Executive Officer of Actelion, commented: “Today’s FDA approval of Uptravi is another major landmark for Actelion. Together with our partners at Nippon Shinyaku we are proud to be able to offer an outstanding oral therapy targeting the prostacyclin pathway. The label for Uptravi recognizes the improvement in long-term outcomes, including reducing the risk of hospitalization for PAH regardless of whether patients received background therapy including an ERA, a PDE-5 inhibitor, or – for the first time ever in PAH – on top of a combination of both, an ERA and a PDE-5 inhibitor.”
Jean-Paul Clozel concluded: “Uptravi will significantly expand the options to delay disease progression after initiation of therapy with a baseline treatment like Opsumit and well ahead of Veletri for the late disease stage. Actelion now has an unparalleled portfolio of treatments across the continuum of care in PAH that offer a combination of long term-efficacy, safety and convenience.”

The safety of Uptravi has been evaluated in a long-term, placebo-controlled study enrolling 1,156 patients with symptomatic PAH (GRIPHON study). The exposure to Uptravi in this trial was up to 4.2 years with median duration of exposure of 1.4 years.

Adverse reactions occurring more frequently on Uptravi compared to placebo by ≥3%, over the course of the study, were headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, flushing, arthralgia, anemia, decreased appetite and rash. These adverse reactions are more frequent during the dose titration phase. Hyperthyroidism was observed in 1% (n=8) of patients on Uptravi and in none of the patients on placebo.

Actelion expects Uptravi to become available to patients in the United States in early January 2016. Outside of the United States, Actelion continues to work with health authorities to obtain regulatory approval for Uptravi.

ABOUT THE GRIPHON STUDY DATA

The Uptravi approval was based in part on data from the long-term, global, Phase III GRIPHON study in 1,156 patients treated for up to 4.2 years. The GRIPHON study, in which more than 80% of patients were already receiving PAH-specific therapies, showed that the risk of the primary composite endpoint was reduced by 40% (p<0.0001) with selexipag compared to placebo.

The benefit of selexipag was consistent across pre-specified patient subgroups such as disease etiology, functional class and baseline PAH therapy, including patients already receiving combination therapy with an ERA and a PDE-5 inhibitor.

Titrating selexipag to an individualized maintenance dose based on tolerability was effective in achieving long-term outcome benefits across the tested dose range. The dosing in GRIPHON was initiated at 200 micrograms (mcg) twice daily (b.i.d) and increased weekly in steps of 200 mcg up to a maximum of 1600 mcg b.i.d. After titrating to the highest tolerated dose, the benefit was consistent across the pre-specified low- (200, 400 mcg b.i.d), medium- (600, 800, 1’000 mcg b.i.d) and high-maintenance (1’200, 1’400, 1’600 mcg b.i.d) dose groups.

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NOTES TO EDITOR:
REGULATORY STATUS OF SELEXIPAG

In December 2014, Actelion submitted the registration dossier for selexipag to both the US FDA and Europe's EMA, where review is ongoing. Submission of the registration dossier to other Health Authorities is ongoing with regulatory reviews underway in Australia, Canada, New Zealand, South Korea, Switzerland, and Taiwan.

ABOUT UPTRAVI® (SELEXIPAG) [1-6]

Uptravi (selexipag), originally discovered and synthesized by Nippon Shinyaku, is a potent, oral, selective IP prostacyclin receptor agonist.

Uptravi and its major metabolite selectively target the prostacyclin receptor (also called IP receptor). The IP receptor is one of 5 major types of prostanoid receptor (IP, EP, DP, TP, FP). Prostacyclin activates the IP receptor to induce vasodilation and inhibit proliferation of vascular smooth muscle cells.

ABOUT THE GRIPHON STUDY

GRIPHON, (Prostacyclin (PGI2) Receptor agonist in Pulmonary arterial Hypertension) was a randomized, multicenter, double-blind, placebo-controlled trial evaluating the long-term efficacy and safety of oral selexipag in patients with PAH.

The GRIPHON study was the largest randomized, controlled, outcome trial ever conducted in PAH patient population, enrolling 1,156 patients in 181 centers from 39 countries in North and Latin America, Europe, and Asia-Pacific. Patients received twice daily administration of selexipag or placebo and were also permitted to receive background PAH-specific therapy of an endothelin receptor antagonist and/or a phosphodiesterase-5 inhibitor when on a stable dose for at least 3 months. At baseline, 80% of patients were receiving oral medication specific for PAH: either an ERA, a PDE-5 inhibitor, or a combination of the two.

This pivotal, event-driven study was designed to demonstrate a prolongation in time to the first morbidity or mortality event for selexipag compared to placebo and to evaluate the safety profile of selexipag in PAH patients. All morbidity and mortality events reported by the investigators were adjudicated by a three person independent Critical Event Committee blinded to the study treatment.

ABOUT THE SAFETY AND TOLERABILITY IN GRIPHON

Overall, 41 (7.1%) patients in the placebo group and 82 (14.3%) in the selexipag group prematurely discontinued treatment due to an adverse event. The most frequent adverse events leading to treatment discontinuation in the selexipag group (>1% difference between selexipag and placebo) were headache (3.3%), diarrhea (2.3%), and nausea (1.7%). Hyperthyroidism occurred in eight selexipag-treated patients and led to treatment discontinuation in one patient. No serious adverse events were reported more frequently (>1% difference between selexipag and placebo) in the selexipag group. Prostacyclin-associated adverse events were more frequent during the titration phase, where they were used to define the individualized highest tolerated dose.

The prostacyclin pathway is one of the 3 best characterized pathways involved in the pathophysiology and treatment of PAH. Prostacyclin is a prostanoid and serves as a signaling molecule in the human body. It is produced, like other vasoactive substances, by endothelial cells. Prostacyclin induces vasodilation, is anti-proliferative, has anti-inflammatory effects and inhibits platelet aggregation. In certain disease conditions, the production of prostacyclin by the endothelium is impaired, allowing for example, the deleterious effects of excessive levels of endothelin or thromboxane to predominate.

PULMONARY ARTERIAL HYPERTENSION (PAH)

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 symptoms of PAH are non-specific and can range from mild breathlessness and fatigue during normal daily activity to symptoms of right heart failure and severe restrictions on exercise capacity and ultimately reduced life expectancy.

PAH is one group within the classification of pulmonary hypertension (PH). This group includes idiopathic PAH, heritable PAH and PAH caused by factors which include connective tissue disease, HIV infection and congenital heart disease.

The last decade has seen significant advances in the understanding of the pathophysiology of PAH, which has been paralleled with developments of treatment guidelines and new therapies. Drugs targeting the three pathways that have been established in the pathogenesis of PAH are endothelin receptor antagonists (ERAs), prostacyclin analogs and phosphodiesterase-5 inhibitors. PAH treatments have transformed the prognosis for PAH patients from symptomatic improvements in exercise tolerance 10 years ago to delayed disease progression today. Improved disease awareness and evidence-based guidelines developed from randomized controlled clinical trial data have highlighted the need for early intervention, goal-oriented treatment and combination therapy.

ABOUT THE ACTELION / NIPPON SHINYAKU ALLIANCE

Actelion and Nippon Shinyaku entered into an exclusive worldwide alliance in April 2008 to collaborate on selexipag, a first orally-available, selective prostacyclin IP receptor agonist for patients suffering from PAH. This compound was originally discovered and synthesized by Nippon Shinyaku. Actelion is responsible for global development and commercialization of selexipag outside Japan, while the two companies will co-develop and co-commercialize in Japan. Nippon Shinyaku will receive milestone payments based on development stage and sales milestones as well as royalties on any sales of selexipag.
ABOUT VALLERIE MCLAUGHLIN, MD

Vallerie V. McLaughlin, MD, is Director of the Pulmonary Hypertension (PH) Program at the University of Michigan Health System and Professor of Internal Medicine at the University of Michigan, Ann Arbor Mich. She is a Fellow of the American College of Cardiology, the American College of Chest Physicians and the American Heart Association, and is a member of the American Thoracic Society. She has served as Chair of the American Heart Association “Women in Cardiology” Committee, Chair of the Scientific Leadership Council of the PH Association, Editor-in-Chief of Advances in Pulmonary Hypertension, Chair of the PH Association Board of Trustees, and Chair of the Medical Education Programs of the PH Association. She was Chair of the American College of Cardiology/American Heart Association Clinical Expert Consensus Document on PH and has served on the American College of Cardiology Scientific Sessions Program Committee. She was inaugurated as a charter member into the Clinical Excellence Society at the University of Michigan. Her research interests focus on PH. Professor McLaughlin was a Steering Committee member to the GRIPHON study and serves as a consultant to Actelion.

References


NIPPON SHINYAKU

For further information on Nippon Shinyaku please visit:

http://www.nippon-shinyaku.co.jp/english/index.html
ACTELION LTD

Actelion Ltd. is a leading biopharmaceutical company focused on the discovery, development and commercialization of innovative drugs for diseases with significant unmet medical needs.

Actelion is a leader in the field of pulmonary arterial hypertension (PAH). Our portfolio of PAH treatments covers the spectrum of disease, from WHO Functional Class (FC) II through to FC IV, with oral, inhaled and intravenous medications. Although not available in all countries, Actelion has treatments approved by health authorities for a number of specialist diseases including Type 1 Gaucher disease, Niemann-Pick type C disease, Digital Ulcers in patients suffering from systemic sclerosis, and mycosis fungoides type cutaneous T-cell lymphoma.

Founded in late 1997, with now over 2,400 dedicated professionals covering all key markets around the world including Europe, the US, Japan, China, Russia and Mexico, Actelion has its corporate headquarters in Allschwil / Basel, Switzerland.

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®). All trademarks are legally protected.

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