Actelion receives Swissmedic approval for Uptravi (selexipag) for treatment of pulmonary arterial hypertension

ALLSCHWIL/BASEL, SWITZERLAND – 16 August 2016 – Actelion Ltd (SIX: ATLN) announced today that Swissmedic has granted approval for the orally active, selective IP prostacyclin receptor agonist Uptravi® (selexipag), originally discovered and synthesized by Nippon Shinyaku, for patients with PAH in Switzerland.

Uptravi is indicated for the treatment of pulmonary arterial hypertension (PAH) in patients with advanced functional limitation (NYHA-functional class III/IV) to delay disease progression.

Uptravi is effective in combination with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor, or in triple combination with an ERA and a PDE-5 inhibitor, or as monotherapy.

Jean-Paul Clozel, Chief Executive Officer of Actelion commented: “The Swissmedic approval represents a major milestone for PAH patients in Switzerland. As a new oral medication that effectively targets the prostacyclin pathway, Uptravi is supported by robust long-term outcome results in combination with an ERA, or a PDE-5 inhibitor, and, for the first time in PAH, in triple combination with both an ERA and a PDE-5 inhibitor. We are now working diligently to make Uptravi available to patients in Switzerland as soon as possible.”

The Swissmedic approval for Uptravi was based on the Phase III GRIPHON study, whose main findings were published in the New England Journal of Medicine in December 2015. This placebo-controlled study, the largest ever in PAH, established the effectiveness, safety and tolerability of Uptravi in patients with PAH. [1]

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NOTES TO THE EDITOR
REGULATORY STATUS OF SELEXIPAG
Market authorization has so far been received in the US (21 December 2015), Canada (21 January 2016), New Zealand (17 March 2016), Australia (18 March 2016), South Korea (11 May 2016), the European Union (12 May 2016) and in Switzerland (15 August 2016). Submission of the registration dossier to other health authorities is ongoing, with regulatory reviews underway in Brazil, Israel, Japan, Singapore, Taiwan and Turkey.

ABOUT UPTRAVI® (SELEXIPAG) [2-7]
Uptravi (selexipag), originally discovered and synthesized by Nippon Shinyaku, is the only approved oral, selective IP receptor agonist targeting the prostacyclin pathway in PAH.

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 [1]
GRIPHON, a global, pivotal Phase III study, was designed to demonstrate a prolongation of time to the first morbidity/mortality event for selexipag compared to placebo and to evaluate the safety of selexipag in PAH patients.

A total of 1'156 patients were randomized to receive placebo or selexipag. Utilizing a dosing scheme that titrated patients up to their individualized doses, 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. If patients were unable to tolerate a dose, the dose was reduced to the previously tolerated dose. A primary endpoint event occurred in 397 patients - 41.6% of those in the placebo group and 27.0% of those in the selexipag group (hazard ratio in the selexipag group as compared with the placebo group, 0.60; 99% confidence interval, 0.46 to 0.78; P<0.001). Disease progression and hospitalization accounted for 81.9% of the events.

At baseline, almost 80% of patients were receiving oral medication specific for PAH: either an ERA, a PDE-5 inhibitor, or a combination of the two. The effect of selexipag with respect to the primary endpoint was similar in the subgroup of patients who were not receiving treatment for the disease at baseline and in the subgroup of patients who were already receiving treatment at baseline (including those who were receiving a combination of both ERA and PDE-5 inhibitor).

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 were more frequent during the dose titration phase. Hyperthyroidism was observed in 1% (n=8) of patients on selexipag and in none of the patients on placebo.

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 receptor agonists, 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. Learn more at http://www.pahuman.com/

ABOUT THE ACTELION / NIPPON SHINYAKU ALLIANCE
In April 2008, Actelion and Nippon Shinyaku entered into an exclusive worldwide alliance, under which 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.

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 2,500 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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implied by such forward-looking statements. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those described herein as anticipated, believed, estimated or expected.