Actelion receives approval for Uptravi (selexipag) for the treatment of pulmonary arterial hypertension in Australia and New Zealand

• Approval granted by Medsafe in New Zealand on 17 March 2016 and by the TGA in Australia on 18 March 2016

ALLSCHWIL, SWITZERLAND – 22 March 2016 – Actelion Ltd (SIX: ATLN) announced today that the Therapeutic Goods Administration (TGA) of Australia and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) have granted approval for the orally active selective IP prostacyclin receptor agonist Uptravi® (selexipag), originally discovered and synthesized by Nippon Shinyaku, for the treatment of pulmonary arterial hypertension.

Uptravi is indicated for the treatment of idiopathic PAH, heritable PAH, PAH associated with connective tissue disease, PAH associated with congenital heart disease with repaired shunts and PAH associated with drugs and toxins, in patients with WHO functional class II, III or IV symptoms.

The labels were based in part 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 of Uptravi in PAH patients with WHO Functional Class II-III symptoms. [1]

Simon Eade, Head of Actelion Asia Pacific Region, commented, “The approval of Uptravi represents a major step forward in disease management for the PAH communities in both Australia and New Zealand. Until now the options for treatments targeting the prostacyclin pathway have been limited, and were burdensome for the patient. Uptravi offers patients an oral treatment that targets the prostacyclin pathway, opening the way for oral combination therapies with proven long-term outcome benefits. We will now work to secure reimbursement and make Uptravi available to patients.”

The safety of selexipag has been evaluated in a long-term, Phase III placebo-controlled study enrolling 1,156 patients with symptomatic PAH. The mean treatment duration was 76.4 weeks.
(median 70.7 weeks) for patients receiving selexipag versus 71.2 weeks (median 63.7 weeks) for patients on placebo. The exposure to selexipag was up to 4.2 years.

The most commonly reported adverse reactions related to the pharmacological effects of Upravi are headache, diarrhoea, nausea and vomiting, jaw pain, myalgia, pain in extremity, arthralgia, and flushing. These reactions are more frequent during the up-titration phase. The majority of these reactions are of mild to moderate intensity.

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NOTES TO EDITOR:

REGULATORY STATUS OF SELEXIPAG
Market authorization has so far been received from the US FDA (21 December 2015) and Health Canada (20 January 2016), New Zealand’s Medsafe (17 March 2016) and Australia’s TGA (18 March 2016). Submission of the registration dossier to other health authorities is ongoing, with regulatory reviews underway in the European Union, Japan, South Korea, Switzerland, Taiwan and Turkey.

ABOUT UPRAVI® (SELEXIPAG) [2-7]
Uptravi (selexipag), originally discovered and synthesized by Nippon Shinyaku, is the only approved oral selective IP receptor agonist administered as tablet, 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 in individualized doses (maximum dose, 1600 mcg twice daily). 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.

Patients received twice daily administration of selexipag or placebo and were also permitted to receive background therapy of endothelin receptor antagonist and/or a phosphodiesterase-5 (PDE-5) inhibitor when on a stable dose for
at least 3 months prior to enrollment. 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 two therapies).

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 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

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.

References


NIPPON SHINYAKU

For further information on Nippon Shinyaku please visit:

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