Actelion receives US FDA approval of Opsumit (macitentan) for the treatment of pulmonary arterial hypertension

ALLSCHWIL, SWITZERLAND – 18 OCTOBER 2013 - Actelion Ltd (SIX: ATLN) announced today that the United States Food and Drug Administration (FDA) has approved the use of the orally available endothelin receptor antagonist Opsumit® (macitentan) 10 mg once daily for the treatment of pulmonary arterial hypertension (PAH) to delay disease progression.

Opsumit is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). Opsumit also reduced hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients were treated with Opsumit® monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

Dr. Vallerie McLaughlin, Director of the Pulmonary Hypertension Program in the Division of Cardiovascular Medicine at the University of Michigan, commented: “Over the past twenty years, great strides have been made in treating PAH patients. However, there has been a medical need for innovative treatments that improve long-term outcomes. Opsumit® is the first clinically proven and only oral treatment option indicated to delay disease progression and reduce the need for PAH hospitalization.”

Dr. McLaughlin concluded: “These effects were demonstrated in SERAPHIN, the first and largest PAH outcome study to date, where Opsumit® was given on average for 2 years, as a monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. I am very pleased that PAH patients will have this new treatment option.”

Jean-Paul Clozel, M.D. and Chief Executive Officer of Actelion commented: “Today’s approval of Opsumit® by the FDA is providing the PAH community with a unique treatment option, the only oral PAH medicine that has proven to delay disease progression. Over the last 14 years, Actelion has worked tirelessly to first discover and then develop Opsumit® in the largest, longest and first-ever outcome study in PAH. I would like to express my gratitude to all the members of the PAH community. Without their contribution, Opsumit® would not have become a reality. We will now leverage our existing PAH expertise and infrastructure to bring Opsumit® to patients within the coming weeks.”
The US label for Opsumit® carries a Boxed Warning alerting patients and health care professionals that the drug should not be used in pregnant women because it can harm the developing fetus. Female patients can receive the drug only through the Opsumit REMS Program. All female patients must be enrolled in the program, comply with pregnancy testing requirements and be counselled regarding the need for contraception.

The most common adverse reactions (more frequent than placebo by ≥3%) observed in patients treated with Opsumit® were anemia, nasopharyngitis/pharyngitis, bronchitis, headache, influenza, and urinary tract infection.

Physicians are advised to measure hemoglobin and liver enzymes prior to initiation of Opsumit® and repeat during treatment as clinically indicated.

In the United States, Actelion expects Opsumit® to become available to patients in November. Outside of the United States, Actelion continues to work with health authorities to obtain regulatory approval for Opsumit®.

The FDA approval was based in part on data from the landmark phase III SERAPHIN study. Published in the New England Journal of Medicine in August 2013, the SERAPHIN study showed the risk of the first occurrence of a morbidity or mortality event, the primary endpoint of the study, was reduced by 45% (p<0.0001) with macitentan 10 mg compared to placebo. This effect was observed irrespective of whether or not patients were already treated with other therapies for PAH. SERAPHIN also showed a risk reduction in PAH related hospitalization and death of 50% (p<0.0001) compared to placebo. [1]

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 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.

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NOTES TO THE EDITOR

ABOUT OPSUMIT®(MACITENTAN)

Opsumit® (macitentan) is a novel dual endothelin receptor antagonist (ERA) that resulted from a tailored drug discovery process with the target of developing an ERA to address efficacy and safety [3].

ABOUT THE SERAPHIN STUDY

SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve clinical outcome) was the largest and longest randomized, controlled study in PAH patients to include a clearly defined morbidity/mortality primary endpoint [2]. The pivotal Phase III study was designed to evaluate the efficacy and safety of Opsumit®(macitentan) - a novel dual endothelin receptor antagonist that resulted from a tailored drug discovery process - through the primary endpoint of time to first morbidity and all-cause mortality event in patients with symptomatic PAH.

Global enrollment was completed in December 2009 with a total of 742 patients. Patients were randomized 1:1:1 to receive two different doses of macitentan (3 mg and 10 mg once daily) or placebo.
Patients were allowed to receive PAH background therapy throughout the study, either PDE-5 inhibitors or oral/inhaled prostanoids. This event-driven study was conducted in 151 centers from almost 40 countries in North America, Latin America, Europe, Asia-Pacific and Africa and was completed in the first half of 2012, with 287 patients having an adjudicated event.

Dr. McLaughlin is a consultant to Actelion and was an investigator in the SERAPHIN trial.

ABOUT SERAPHIN STUDY DATA
Patients were randomized to placebo (n=250), macitentan 3 mg (n=250), or macitentan 10 mg (n=242). The primary end point occurred in 46.4%, 38.0%, and 31.4% of the patients in these groups, respectively. The hazard ratio for macitentan 3 mg versus placebo was 0.70 (97.5% CI, 0.52 to 0.96; p=0.0108) and the hazard ratio for macitentan 10 mg versus placebo was 0.55 (97.5% CI, 0.39 to 0.76; p<0.0001). Worsening of pulmonary arterial hypertension was the most frequent primary end point event. The effect of macitentan on this end point was observed irrespective of background therapy for pulmonary arterial hypertension. [1]

ABOUT THE SAFETY AND TOLERABILITY PROFILE
Opsumit is contraindicated in pregnancy because it may harm the developing fetus. Females of reproductive potential should be counselled on the use of reliable contraception and have a negative pregnancy test prior to initiating therapy and monthly thereafter.

Other ERAs have been associated with elevations of aminotransferases, hepatotoxicity, and liver failure. Liver enzyme tests should be obtained prior to initiation of Opsumit® and repeated during treatment as clinically indicated. If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by clinical symptoms of hepatotoxicity, discontinue Opsumit®.

Decreases in hemoglobin concentration and hematocrit occurred following administration of other ERAs and were observed in clinical studies with OPSUMIT. The decreases occurred early and stabilized thereafter. Decreases in hemoglobin seldom require transfusion. Initiation of Opsumit® is not recommended in patients with severe anemia. Hemoglobin should be measured prior to initiation of treatment and repeat during treatment as clinically indicated.

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue Opsumit®.

Other ERAs have been associated with adverse effects on spermatogenesis. Men should be counseled about potential effects on fertility.

The use of Opsumit® with strong CYP3A4 inducers or inhibitors should be avoided.

The most common adverse reactions (more frequent than placebo by ≥3%) observed in patients treated with Opsumit were anemia, nasopharyngitis/pharyngitis, bronchitis, headache, influenza, and urinary tract infection.

ABOUT OPSUMIT® (MACITENTAN) SUBMISSIONS TO HEALTHCARE AUTHORITIES
Approval of the new drug application for Opsumit® (macitentan) was issued by the US Food and Drug Administration (FDA) on 18 October 2013 for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk
distance, worsened PAH symptoms and need for additional PAH treatment). The need for PAH hospitalization was also reduced.

Regulatory reviews are ongoing in Europe, Canada, Switzerland, Australia, Taiwan, Korea and Mexico.

ABOUT PULMONARY ARTERIAL HYPERTENSION [9, 10]
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 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), prostacyclins 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.

In PAH, survival rates are unacceptably low and PAH remains incurable.

References


Actelion Ltd
Actelion Ltd is a biopharmaceutical company with its corporate headquarters in Allschwil/Basel, Switzerland. Actelion's first drug Tracleer® (bosentan), an orally available dual endothelin receptor antagonist, has been approved as a therapy for pulmonary arterial hypertension. Actelion markets Tracleer through its own subsidiaries in key markets worldwide, including the United States (based in South San Francisco), the European Union, Japan, Canada, Australia and Switzerland. Actelion, founded in late 1997, is a leading player in innovative science related to the endothelium - the single layer of cells separating every blood vessel from the blood stream. Actelion's over 2,300 employees focus on the discovery, development and marketing of innovative drugs for significant unmet medical needs. 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®).

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