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New OPSUMIT® (macitentan) Data Show Initial Combination Therapy with Tadalafil Improved Hemodynamic Clinical and Functional Parameters in Patients with Pulmonary Arterial Hypertension

OPSUMIT, as part of a combination regimen, reduced the primary endpoint of mean pulmonary vascular resistance by 47% at week 16 compared with baseline

NEW ORLEANS – October 21, 2019 – Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical Company of Johnson & Johnson, today announces new data evaluating initial combination therapy with OPSUMIT® (macitentan) and tadalafIl, a PDE5 inhibitor. Patients with pulmonary arterial hypertension (PAH, WHO Group 1) taking this combination showed hemodynamic improvement, as well as improvements in functional parameters and risk profiles. The combination was also well tolerated in these patients. The study data is being shared today at the CHEST Annual Meeting 2019, held October 19-23 in New Orleans, Louisiana.

The OPTIMA (c**O**mbination thera**P**y of maci**T**entan and tadalaf**I**l in patients with newly diagnosed pul**M**onary **A**rterial Hypertension) study was a prospective, multicenter, single-arm, open-label, Phase IV trial evaluating the efficacy, safety, and tolerability of initial oral combination therapy with OPSUMIT and tadalafil in patients with newly diagnosed PAH. A total of 46 patients were enrolled in the study.

“OPSUMIT, in combination with tadalafil, showed a 47% reduction of the primary endpoint of mean pulmonary vascular resistance (PVR) at week 16 compared with baseline in patients with PAH,” said Olivier Sitbon, M.D., Ph.D., principal investigator and professor of respiratory medicine at Université Paris-Sud. “These data are meaningful because improvement of PVR, an important indicator of right ventricular function, is a key treatment goal. Current clinical guidelines for PAH recommend upfront double oral combination therapy and this study confirms that initial oral dual combination with macitentan and tadalafil is beneficial in those patients.”

Safety and tolerability findings were consistent with previous clinical trials that supported the approval and use of OPSUMIT 10mg once-daily. The most common adverse events (AEs) in the OPTIMA study were peripheral edema (28.3%), headache (23.9%), diarrhea (19.6%), dyspnea (15.2%), anemia (13.0%) and asthenia (13.0%). Four patients had a decrease in hemoglobin below 10 g/dL and one patient had aminotransferases ≥3 times the upper limit of normal. Three patients discontinued treatment due to AEs and three patients died during the study. Causes of death were cardiac arrest, heart failure, and multiorgan failure with sepsis.[1]

PAH is a specific form of pulmonary hypertension (PH) in which the walls of the pulmonary arteries (blood vessels leading from the right side of the heart to the lungs) become thick and stiff, narrowing the space for blood to flow, which increases blood pressure.[2,3] Despite recent advances, PAH is a serious, progressive disease with no cure, and one in three patients die within five years of diagnosis.[4,5] Risk assessment in PAH is an important tool for monitoring disease progression and response to therapy. The main treatment goal is to achieve and maintain low-risk status.[6]

"The results of the OPTIMA study provide valuable insights about the safety and efficacy of OPSUMIT in combination with a PDE5 inhibitor and add to the body of evidence supporting combination therapy as the standard of care," said Alessandro Maresta, M.D., Vice President and Head of Medical Affairs at Actelion Pharmaceuticals Ltd. "PAH continues to have a devastating impact on people's lives and our focus is on researching and developing innovative medicines that improve the lives of these patients."

OPSUMIT is indicated for the treatment of PAH (WHO Group I) to reduce the risks of disease progression and hospitalization for PAH. 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.[7]

** Dr. Sitbon has received research support from Actelion and has served as a paid consultant to the company.*

ABOUT PULMONARY ARTERIAL HYPERTENSION (PAH)
PAH is a specific form of PH that causes the walls of the pulmonary arteries (blood vessels leading from the right side of the heart to the lungs) to become thick and stiff, narrowing the space for blood to flow, and causing an increased blood pressure to develop within the lungs. PAH is a serious, progressive disease with a variety of etiologies, and has a major impact on patients' functioning, as well as their physical, psychological and social wellbeing. There is currently no cure for PH and it is often fatal.[4,8,9] However, the last decade has seen significant advances in the understanding of the pathophysiology of PAH, transforming the prognosis for PAH patients from symptomatic improvements in exercise tolerance 10 years ago, to delayed disease progression today.

ABOUT THE OPTIMA STUDY
OPTIMA was a prospective, multicenter, single-arm, open-label, Phase IV trial evaluating the efficacy, safety and tolerability of initial oral combination therapy with OPSUMIT and tadalafil in patients with newly diagnosed PAH. A total of 46 patients were enrolled and treated (all 46 are included in the efficacy and safety analyses). In the OPTIMA study, the primary endpoint of mean PVR was reduced by 47% at week 16 compared with baseline in newly diagnosed patients with pulmonary arterial hypertension (geometric mean of the ratio week 16 to baseline 0.53; 95% CI 0.47, 0.59). Results showed hemodynamic improvement, as well as improvements in functional parameters including 6-minute walk distance, and risk profile. Safety and tolerability findings were consistent with previous clinical trials that supported the approval and use of OPSUMIT 10 mg once-daily.[1]

What is OPSUMIT® (macitentan)?
OPSUMIT is a prescription medicine used to treat pulmonary arterial hypertension (PAH, WHO Group 1). PAH is high blood pressure in the arteries of your lungs. OPSUMIT can:

- Improve your ability to exercise as measured by the 6-minute walk distance (6MWD). In a clinical study of mainly WHO FC II-III patients, those taking OPSUMIT walked, on average, 22 meters farther at Month 6 than patients not taking it
- Improve some of your symptoms
- Help slow down the progression of your disease
- Lower your chance of being hospitalized for PAH

It is not known if OPSUMIT is safe and effective in children.

The most important information about OPSUMIT® (macitentan)

Do not take OPSUMIT if you are pregnant or trying to get pregnant. OPSUMIT can cause serious birth defects if taken while pregnant.

Women who are able to get pregnant must have negative pregnancy tests:

- Before starting OPSUMIT
- Each month while taking OPSUMIT
- For 1 month after stopping OPSUMIT

Your doctor will decide when you should take pregnancy tests.

You are medically able to get pregnant if you are a woman who fits all of the following guidelines:

- has started puberty, even if you have not had a menstrual period yet
- has a uterus
- has not gone through menopause (menopause means you have not had a menstrual period for at least 12 months for natural reasons, or have had your ovaries removed)

You are not medically able to get pregnant if you are a woman who fits at least 1 of the following guidelines:

- has not started puberty
- does not have a uterus
- has gone through menopause (you have not had a menstrual period for at least 12 months for natural reasons, or have had your ovaries removed)
- is infertile for other medical reasons and this infertility is permanent and cannot be reversed

While taking OPSUMIT, and for 1 month after stopping OPSUMIT, women who are able to get pregnant must use 2 acceptable forms of birth control. Women who have had a tubal sterilization, a progesterone implant, or have an IUD (intrauterine device) do not need a second form of birth control. Talk to your doctor or gynecologist about which birth control to use while on OPSUMIT. If you decide to change your form of birth control, talk with your doctor or gynecologist. This way you can be sure to choose another acceptable form of birth control. **Also review the Medication Guide for acceptable birth control options.**

It's important not to have unprotected sex while taking OPSUMIT. Tell your doctor right away if you have unprotected sex, think your birth control has failed, miss a menstrual period, or think you may be pregnant. He or she may recommend using a form of emergency birth control.

If you are the parent or caregiver of a female child who started taking OPSUMIT before reaching puberty, check with your child regularly for any signs of puberty. **Your child may reach puberty before having her first menstrual period.** Talk to your doctor if you think your child is showing signs of puberty or if you have any questions about the signs of puberty.

Before starting OPSUMIT, women must enroll in a program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS). If you are a woman who is able to get pregnant, you must talk to your doctor to learn the benefits and risks of OPSUMIT. You must also agree to all of the instructions in the program. Men who are prescribed OPSUMIT do not need to enroll in this program.

Who should not take OPSUMIT?

Do not take OPSUMIT if you are pregnant, plan to become pregnant, or become pregnant during treatment with OPSUMIT. OPSUMIT can cause serious birth defects. See "The most important information about OPSUMIT."

Talk to your doctor about all your medical conditions, as well as all the medicines, vitamins, and supplements you take. OPSUMIT and other medicines may affect each other causing side effects. Tell your doctor right away if you take an HIV medicine. Do not start any new medicine until you check with your doctor.

What should I avoid while taking OPSUMIT?

- **Do not get pregnant**. OPSUMIT can cause serious birth defects. See "The most important information about OPSUMIT." If you miss a menstrual period or think you may be pregnant, call your doctor right away
- **You should not breastfeed if you take OPSUMIT**. It is not known if OPSUMIT passes into your breast milk. Talk to your doctor about the best way to feed your baby

What are the possible side effects of OPSUMIT?
OPSUMIT can cause serious side effects, including:

- **Serious birth defects**. See "The most important information about OPSUMIT"
- **Some medicines that are like OPSUMIT can cause liver problems**. Your doctor should do blood tests to check your liver before you start OPSUMIT. Tell your doctor if you have any of these symptoms, which could be a sign of liver problems while on OPSUMIT:
    - Nausea or vomiting
    - Pain in the upper right stomach
    - Feeling tired
    - Loss of appetite
    - Your skin or the whites of your eyes turn yellow
    - Dark urine
    - Fever
    - Itching
- **Fluid retention** could happen during the first weeks after starting OPSUMIT. Tell your doctor right away if you notice unusual weight gain or swelling in your ankles or legs. Your doctor will look for the cause
- **Low red blood cell levels (anemia) can happen while taking OPSUMIT, usually during the first weeks after starting OPSUMIT. In some cases a blood transfusion may be needed, but this is not common**. Your doctor will do blood tests to check for anemia before you start OPSUMIT. You may also need to do these blood tests while taking OPSUMIT
- **Decreased sperm counts**. OPSUMIT, and other medicines like OPSUMIT, may cause decreased sperm counts in men who take these medicines. If fathering a child is important to you, tell your doctor

The most common side effects are:

- Stuffy nose or sore throat
- Irritation of the airways (bronchitis)
- Headache
- Flu
- Urinary tract infection

Talk to your doctor if you have a side effect that bothers you or does not go away. These are not all the possible side effects of OPSUMIT. For more information, ask your doctor or pharmacist.

You may report side effects to FDA at **1-800-FDA-1088** or **www.fda.gov/medwatch.**

Please see full Prescribing Information and Medication Guide, including an Important Warning about Serious Birth Defects at http://opsumit.com/opsumit-prescribing-information.pdf.

ABOUT ACTELION
In June 2017, Actelion became part of the Janssen Pharmaceutical Companies of Johnson & Johnson. Actelion's medicines have helped to expand and strengthen Janssen's portfolio with leading, differentiated in-market medicines and promising late-stage compounds. Janssen has added Pulmonary Hypertension as a therapeutic area of focus to maintain the leadership position Actelion has built in this important disease area. Learn more at www.actelion.com. Follow us on Twitter @actelion_com.

ABOUT THE JANSSEN PHARMACEUTICAL COMPANIES OF JOHNSON & JOHNSON
At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular & Metabolism, Immunology, Infectious Diseases & Vaccines, Neuroscience, Oncology and Pulmonary Hypertension. Learn more at www.janssen.com. Follow us at www.twitter.com/JanssenGlobal. Actelion Pharmaceuticals Ltd is one of the Janssen Pharmaceutical Companies of Johnson & Johnson.

CAUTIONS CONCERNING FORWARD-LOOKING STATEMENTS

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding the development of OPSUMIT® (macitentan). The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Actelion Pharmaceuticals US, Inc., any of the other Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended December 30, 2018, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's most recently filed Quarterly Report on Form 10-Q, and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

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