News Release

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Janssen Submits New Drug Application to U.S. FDA Seeking Approval of Investigational Single Tablet Combination Therapy of Macitentan and Tadalafil for Treatment of Patients with Pulmonary Arterial Hypertension (PAH)

This is the first and only single tablet combination therapy application to be submitted for review in the U.S. for this rare, progressive disease

If approved, Janssen's comprehensive PAH portfolio has the potential to cover all guidelines-recommended treatment pathways

RARITAN, NJ, May 30, 2023 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today the submission of a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) seeking approval of an investigational single tablet combination therapy of macitentan 10mg and tadalafil 40mg (M/T STCT) for the long-term treatment of pulmonary arterial hypertension (PAH, World Health Organization [WHO] Group 1) in adult patients with WHO functional class (FC) II-III.[1] The application is based on positive data from the Phase 3 A DUE study, which met its primary endpoint and demonstrated that M/T STCT significantly improved pulmonary hemodynamics (blood flow through

[1] WHO FC II/III is defined as slight or marked limitation of physical activity with ordinary or less than ordinary activity causing undue shortness of breath or fatigue, chest pain, or near fainting.

pulmonary blood vessels) versus macitentan and tadalafil monotherapies in this PAH patient population.

"People with PAH are often prescribed numerous medicines to manage their condition, so the potential to offer a single tablet combination of two guideline-recommended therapies could not only decrease pill burden but may also help improve the patient treatment experience and clinical outcomes," said James F. List, M.D., Ph.D., Global Therapeutic Area Head, whose team oversees a portfolio of programs including Pulmonary Hypertension at Janssen Research & Development, LLC. "Today's submission builds on our decades-long commitment to address patient needs and bring forward medicines with the potential to offer an improved standard of PAH care."

PAH is a rare, progressive and life-threatening blood vessel disorder characterized by the constriction of small pulmonary arteries and elevated blood pressure in the pulmonary circulation that eventually leads to right heart failure.[2] The latest European Society of Cardiology/European Respiratory Society (ESC/ERS) PH guidelines[i] recommend initial double combination therapy with macitentan and tadalafil for PAH patients without cardiopulmonary comorbidities. Currently, this requires patients to take multiple pills as no single tablet that combines two or more PAH-specific pathways is available for these patients.[3]

The NDA is based on late-breaking data from the Phase 3 A DUE study, which met its co-primary endpoints, demonstrating marked pulmonary hemodynamic improvement. The safety profile of M/T STCT was consistent with the safety profile of the individual components, macitentan and tadalafil[ii,iii]. The open label arm of the A DUE study is ongoing.

[2] Right heart failure occurs when the heart's right ventricle is too weak to pump enough blood to the lungs.
[3] OPSYNVI® (macitentan 10mg and tadalafil 40mg) was approved in Canada in October 2021 and in Argentina in October 2022 but only for substitution indication (for PAH patients who are already treated with combination of macitentan 10mg and tadalafil 40mg as separate tablets) based on bioequivalence studies.

About the single tablet combination therapy (macitentan 10mg and tadalafil 40mg)

M/T STCT is the first investigational, single tablet combination therapy that combines the endothelin receptor antagonist (ERA) macitentan and the phosphodiesterase type 5 inhibitor (PDE5i) tadalafil for once daily administration.

About the A DUE Study

The A DUE study is a double-blind, randomized, active-controlled, multi-center, adaptive parallel-group study designed to compare the efficacy and safety of investigational M/T STCT versus macitentan and tadalafil monotherapies in patients with PAH. A total of 187 adult PAH patients from across 148 sites in 19 countries worldwide in WHO FC II or III who were treatment naïve or on a stable dose of an ERA or a PDE5i for at least three months, were enrolled in the study. The primary endpoint is pulmonary vascular resistance (PVR) measured 16 weeks following initiation of treatment expressed as the ratio of geometric means to baseline.

About tadalafil

Tadalafil is a PDE5i indicated for the treatment of PAH (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II – III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

What is OPSUMIT®?

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 <u>are medically able</u> to get pregnant if you are a woman who fits <u>all</u> 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 <u>are not medically able</u> to get pregnant if you are a woman who fits <u>at least 1</u> 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®."

Do not take OPSUMIT® if you are allergic to macitentan or any of the ingredients in OPSUMIT®. See the Medication Guide for a complete list of ingredients in 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 https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/OPSUMIT-pi.pdf.

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 & Retina; Immunology; Infectious Diseases & Vaccines; Neuroscience; Oncology; and Pulmonary Hypertension.

Learn more at www.janssen.com. Follow us at @JanssenGlobal and @JanssenUS. Janssen Research & Development, LLC is part 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 product development and the potential benefits and treatment impact of macitentan/tadalafil STCT. 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 Janssen Research & Development, LLC 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; competition, including technological advances, new products and patents attained by competitors; challenges to patents; 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 January 1, 2023, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in

Johnson & Johnson's subsequent Quarterly Reports on Form 10-Q and other 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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[i] 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal (2022) 43, 3618–3731. https://doi.org/10.1093/eurheartj/ehac237.

[ii] ADCIRCA (tadalafil) Prescribing Information. https://pi.lilly.com/us/adcirca-pi.pdf

[iii] OPSUMIT (macitentan) Prescribing Information. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/OPSUMIT-pi.pdf