Johnson&Johnson

Press Release

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U.S. FDA Approves OPSYNVI® (macitentan and tadalafil) as the First and Only Once-Daily Single-Tablet Combination Therapy for Patients with Pulmonary Arterial Hypertension (PAH)

OPSYNVI® combines two proven treatments with established efficacy and safety profiles into one tablet to be taken once daily, offering an option that helps to support the implementation of clinical guideline recommendations for early use of combination therapy.[1]

The comprehensive PAH portfolio at Johnson & Johnson now includes treatments that address all three foundational and guideline-recommended pathways for this rare, progressive disease.[2]

Approval is based on the results from the pivotal Phase 3 A DUE study, which met its co-primary endpoints, demonstrating significant pulmonary hemodynamic improvement.[1]

RARITAN, NJ, March 22, 2024 – Johnson & Johnson today announced that the U.S. Food and Drug Administration (FDA) has approved OPSYNVI® – a single-tablet combination of macitentan, an endothelin receptor antagonist (ERA), and tadalafil, a phosphodiesterase 5 (PDE5) inhibitor – for the chronic treatment of adults with pulmonary arterial hypertension (PAH, World Health Organization [WHO] Group I) and WHO functional class (FC) II-III.[1] OPSYNVI® may be used in patients with PAH who are treatment-naïve or who are already on an ERA, PDE5 inhibitor or both. OPSYNVI® may be used in patients who are currently treated concomitantly with stable doses of macitentan 10 mg and tadalafil 40 mg (20 mg x 2) as separate tablets.[1]

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] An estimated 500 to 1,000 new cases of PAH are diagnosed each year in the U.S., classifying the disease as a rare condition.[3]

The 2022 European Society of Cardiology (ESC) / European Respiratory Society (ERS) clinical guidelines recommend initial combination therapy of an ERA and a PDE5 inhibitor for patients with idiopathic PAH, heritable drug-associated PAH, or PAH-associated with connective tissue disease without cardiopulmonary comorbidities at low or intermediate risk.[2]

“Clinical guidelines recommend treating patients with initial and sequential dual-combination therapy, regardless of risk at initial diagnosis and follow-up. Historically, this required patients to take multiple pills because no single-tablet combination therapy targeting two or more pathways was available,” said Kelly Chin, M.D., Professor of Internal Medicine and Director of the Pulmonary Hypertension Program at UT Southwestern Medical Center, and an investigator in the A DUE study.* “As administration of macitentan and tadalafil together are commonly prescribed for initial therapy for PAH, the introduction of a single tablet combining both is promising for clinicians treating patients as it may help bridge the gap between clinical guidelines and everyday clinical practice, while offering a patient-friendly approach to support initial combination therapy and rapid escalation for the appropriate patients.”

The FDA’s approval of OPSYNVI® is based on the results from the pivotal Phase 3 A DUE study, in which OPSYNVI® demonstrated greater reduction in Pulmonary Vascular Resistance (PVR) after 16 weeks versus tadalafil or macitentan monotherapy. OPSYNVI® has a Boxed Warning due to the risk of embryo-fetal toxicity and requires female patients to enroll in the Macitentan-Containing Products Risk Evaluation and Mitigation Strategy (REMS) program.[1]

With the approval, Johnson & Johnson now offers a PAH portfolio addressing all three foundational and guideline-recommended pathways – nitric oxide, endothelin, and prostacyclin.

“People with PAH often live with the burden of taking many pills each day, which can pose challenges,” said James F. List, M.D., Ph.D., Global Therapeutic Area Head, whose team oversees a portfolio of programs including Pulmonary Hypertension at Johnson & Johnson. “We’re thrilled to bring this single tablet combination therapy to patients, as it has the potential to optimize disease management and fulfill a significant unmet need in supporting recently updated treatment guidelines that call for initial or early combination treatment.”

About OPSYNVI®[1]

OPSYNVI® is a combination of macitentan, an endothelin receptor antagonist (ERA), and tadalafil, a phosphodiesterase 5 (PDE5) inhibitor indicated for the chronic treatment of pulmonary arterial hypertension (PAH, WHO Group I) in adult patients of WHO functional class (FC) II-III.

Individually, macitentan reduces the risk of clinical worsening events and hospitalization, and tadalafil improves exercise ability.

About the A DUE Study[1,4]

The A DUE study was a double-blind, randomized, active-controlled, multi-center, adaptive, parallel-group study designed to compare the efficacy and safety of OPSYNVI® to macitentan and tadalafil monotherapies in adult patients with PAH (WHO FC II or III). The three-arm trial enrolled patients from across 76 sites in 16 countries/territories worldwide who were treatment-naïve or on a stable dose of an endothelin receptor antagonist (ERA), or a phosphodiesterase 5 (PDE5) inhibitor, for at least three months. The primary endpoint was change from baseline in PVR at the end of double-blind treatment at 16 weeks and was considered met if macitentan and tadalafil fixed-dose combination (FDC) treatment was superior to both monotherapies. Following the treatment period, patients transitioned to the open-label treatment period for 24 months.

INDICATION

OPSYNVI® is the combination of macitentan and tadalafil indicated for the chronic treatment of adults with pulmonary arterial hypertension (PAH, WHO Group I and WHO Functional Class [FC] II-III).

Individually, macitentan reduces the risk of clinical worsening events and hospitalization, and tadalafil improves exercise ability.

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

- **Do not administer OPSYNVI® to a pregnant female because it may cause fetal harm.**
- **Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.**
- **For all female patients, OPSYNVI® is available only through a restricted program called the Macitentan-Containing Products Risk Evaluation and Mitigation Strategy (REMS).**

CONTRAINDICATIONS

- **Pregnancy:** OPSYNVI® may cause fetal harm when administered to a pregnant woman and is contraindicated in females who are pregnant. If OPSYNVI® is used during pregnancy, advise the patient of the potential risk to a fetus.
- **Hypersensitivity:** OPSYNVI® is contraindicated in patients with a history of a hypersensitivity reaction to macitentan, tadalafil, or any component of the product.
- **Concomitant Organic Nitrates:** OPSYNVI® is contraindicated in patients who are using any form of organic nitrate, either regularly or intermittently. Do not use nitrates within 48 hours of the last dose of OPSYNVI®.
- **Concomitant Guanylate Cyclase (GC) Stimulators:** OPSYNVI® is contraindicated in patients using GC stimulators such as riociguat.

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity and Macitentan-Containing Products REMS:

Due to the risk of embryo-fetal toxicity, OPSYNVI® is available for females only through a restricted program called the Macitentan-Containing Products REMS Program. For females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods, and obtain monthly pregnancy tests.

Notable requirements of the Macitentan-Containing Products REMS Program include:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Macitentan-Containing Products REMS Program prior to initiating OPSYNVI®. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSYNVI®.

Hepatotoxicity

- ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure.
- In the double-blind arm of the A DUE study, the incidence of elevated aminotransferases >3 x ULN was 1.0%, and >8 x ULN was 1.0% for OPSYNVI®. In the combined double-blind/open-label arm, the incidence was 3.4% and 1.1%, respectively.
- Discontinuations for hepatic adverse events in the double-blind and combined double-blind/open-label arms study for OPSYNVI® were 0.9% and 2.2%, respectively.
- Obtain liver enzyme tests prior to initiation of OPSYNVI® and repeat during treatment as clinically indicated.
- Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching). If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 x ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSYNVI®. Consider re-initiation of OPSYNVI® when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.
- Do not initiate OPSYNVI® in patients with elevated aminotransferases (> 3 x ULN) at baseline. Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied; therefore, avoid use of OPSYNVI®.

Hypotension

- OPSYNVI® has vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing OPSYNVI®, physicians should carefully consider whether patients with underlying cardiovascular disease could be adversely affected by such vasodilatory effects. Patients with pre-existing hypotension, autonomic dysfunction, or left ventricular outflow obstruction, may be particularly sensitive to the actions of vasodilators.

Hemoglobin Decrease

- Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and were observed in clinical studies with OPSYNVI® and OPSUMIT®. These decreases occurred early and stabilized thereafter.
- In the placebo-controlled study of OPSUMIT® in PAH, OPSUMIT® 10 mg caused a mean decrease in hemoglobin from baseline to up to 18 months of about 1.0 g/dL compared to no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT® 10 mg group and in 3.4% of the placebo group. Similar results were observed in the trial with OPSYNVI®.
- Decreases in hemoglobin seldom require transfusion. Initiation of OPSYNVI® is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated.

Worsening Pulmonary Veno-Occlusive Disease (PVOD)

- Since there are no clinical data on administration of OPSYNVI® tablets to patients with veno-occlusive disease, administration of OPSYNVI® tablets to such patients is not recommended. Should signs of pulmonary edema occur when OPSYNVI® tablets are administered, the possibility of associated PVOD should be considered. If confirmed, discontinue OPSYNVI®.

Visual Loss and Hearing Impairment
- Non–arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including tadalafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION.
- Use of OPSYNVI® in patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, is not recommended.
- Cases of sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness, have been reported in patients taking tadalafil.

Fluid Retention
- Peripheral edema and fluid retention are known clinical consequences of PAH and known effects of ERAs, and heart failure has been reported in patients taking OPSYNVI®. In the clinical study of OPSYNVI® in PAH, the incidence of peripheral edema/fluid retention was 20.6% in the active-controlled and 17.3% in the double-blind/open-label arm.
- Patients with underlying left ventricular dysfunction may be at particular risk for developing significant fluid retention after initiation of ERA treatment.
- Monitor for signs of fluid retention after OPSYNVI® initiation. If clinically significant fluid retention develops, evaluate the patient to determine the cause, such as OPSYNVI® or underlying heart failure, and the possible need to discontinue OPSYNVI®.

Combination With Other PDE5 Inhibitors
- Tadalafil, a PDE5 inhibitor and a component of OPSYNVI®, is also indicated for erectile dysfunction. Instruct patients taking OPSYNVI® tablets not to take other PDE5 inhibitors.

Decreased Sperm Counts and Prolonged Erection
- Macitentan may have an adverse effect on spermatogenesis. Counsel men about potential effects on fertility.
- There have been reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for PDE5 inhibitors like tadalafil. Patients with conditions that might predispose them to priapism, or in patients with anatomical deformation of the penis are at an increased risk. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention.

ADVERSE REACTIONS
- The most common adverse reactions (occurring in ≥ 10% of the OPSYNVI®-treated patients) from the double-blind study data were edema/fluid retention (21%), anemia (19%), and headache/migraine (18%). The incidence of treatment discontinuations due to adverse events among patients receiving OPSYNVI® in the double-blind phase of the study was 8%. The most frequent adverse reactions leading to discontinuation were anemia and hemoglobin decreased (2% grouped) and peripheral edema and peripheral swelling (2% grouped).

DRUG INTERACTIONS
- **Nitrates:** Administration of nitrates within 48 hours after the last dose of OPSYNVI® is contraindicated.
- **Strong CYP3A4 Inducers:** Strong inducers of CYP3A4, such as rifampin, significantly reduce macitentan exposure. Use of OPSYNVI® with strong CYP3A4 inducers should be avoided.
- **Strong CYP3A4 Inhibitors:** Concomitant use of strong CYP3A4 inhibitors like ketoconazole, increases exposure to both macitentan and tadalafil. Avoid concomitant use of OPSYNVI® with strong

CYP3A4 inhibitors such as ritonavir, ketoconazole and itraconazole. Use other PAH treatment options when strong CYP3A4 inhibitors are needed.

- **Moderate Dual or Combined CYP3A4 and CYP2C9 Inhibitors:**
  - Concomitant use of moderate dual inhibitors of CYP3A4 and CYP2C9 such as fluconazole, is predicted to increase macitentan exposure approximately 4-fold. Avoid concomitant use of OPSYNVI® with moderate dual inhibitors of CYP3A4 and CYP2C9 (such as fluconazole and amiodarone).
  - Concomitant treatment of both a moderate CYP3A4 inhibitor and moderate CYP2C9 inhibitor with OPSYNVI® should be avoided.
- **Alpha-Blockers:** PDE5 inhibitors, including tadalafil, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure lowering effects. Therefore, the combination of OPSYNVI® and doxazosin is not recommended.
- **Antihypertensives:** PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. Small reductions in blood pressure occurred following coadministration of tadalafil with selected antihypertensive medications compared with placebo.
- **Alcohol:** Substantial consumption of alcohol in combination with OPSYNVI® can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache.

USE IN SPECIFIC POPULATIONS

Pregnancy

- OPSYNVI® is contraindicated during pregnancy. Macitentan, a component of OPSYNVI®, may cause embryo-fetal toxicity, including birth defects and fetal death, when administered to a pregnant female.
- If the patient becomes pregnant while taking this drug, advise the patient of the risk to a fetus.

Lactation

- There are no data on the presence of tadalafil, macitentan, and/or their metabolites in human milk, the effects on the breastfed infant, or the effect on milk production. Because of the potential for serious adverse reactions in breastfed infants from OPSYNVI®, advise women not to breastfeed during treatment with OPSYNVI®.

Females and Males of Reproductive Potential

- **Pregnancy Testing:** Verify the pregnancy status of females of reproductive potential prior to initiating OPSYNVI®, monthly during treatment and one month after stopping treatment with OPSYNVI®. The patient should contact her physician immediately for pregnancy testing if onset of menses is delayed or pregnancy is suspected. If the pregnancy test is positive, the physician and patient must discuss the risks to her, the pregnancy, and the fetus.

- **Contraception:** Female patients must choose one highly effective form of contraception (intrauterine devices [IUD]), contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods) during treatment with OPSYNVI® and for 1 month after treatment with OPSYNVI®. If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method.

- **Male Infertility:** Based on findings in animals, macitentan may impair fertility in males of reproductive potential. There have been no studies evaluating the effect of tadalafil on fertility in men or women.

Pediatric Use

- The safety and efficacy of OPSYNVI® in children has not been established.

Renal Impairment

- The use of OPSYNVI® is not recommended in patients undergoing dialysis. Avoid use of OPSYNVI® in patients with severe renal impairment (creatinine clearance 15-29 mL/min).

Hepatic Impairment

- OPSYNVI® must not be initiated in patients with severe hepatic impairment, or clinically significant elevated hepatic aminotransferases (> 3 × ULN).

Please read Important Safety Information and full Prescribing Information, including Boxed WARNING, for OPSYNVI®.

About Johnson & Johnson

At Johnson & Johnson, we believe health is everything. Our strength in healthcare innovation empowers us to build a world where complex diseases are prevented, treated, and cured, where treatments are smarter and less invasive, and solutions are personal. Through our expertise in Innovative Medicine and MedTech, we are uniquely positioned to innovate across the full spectrum of healthcare solutions today to deliver the breakthroughs of tomorrow, and profoundly impact health for humanity. Learn more at https://www.jnj.com/ or at www.janssen.com/johnson-johnson-innovative-medicine. Follow us at @JanssenUS and @JNJInnovMed. Janssen Research & Development, LLC and Actelion Pharmaceuticals US, Inc., are both Johnson & Johnson companies.

[*]Dr. Chin was compensated for her participation on the steering committee for the A DUE study.

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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 OPSYNVI®. 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; Actelion Pharmaceuticals US, Inc., 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 December 31, 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 Janssen Research & Development, LLC, Actelion Pharmaceuticals US, Inc. nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

1. OPSYNVI® Prescribing Information. Titusville, NJ: Actelion Pharmaceuticals US, Inc.
2. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43(38):3618-3731.
3. American Lung Association, PAH, 23.10.2020, "Learn About Pulmonary Arterial Hypertension", lung.org, https://www.lung.org/lung-health-diseases/lung-disease-lookup/pulmonary-arterial-hypertension/learn-about-pulmonary-arterial-hypertension.
4. Grünig E, et al. *JACC*. 2024; 83(4): 473-484. DOI:10.1016/j.jacc.2023.10.045.

