For the chronic treatment of adults with pulmonary arterial hypertension (PAH, WHO Group I and WHO Functional Class [FC] II-III)[1]

Once-Daily OPSYNVI® Is the First and Only US FDA-Approved Single-Tablet Combination of Macitentan+Tadalafil[1,2]

OPSYNVI® contains 2 proven PAH therapies in 1 tablet[1,3,4]

OPSYNVI® (macitentan/tadalafil) targets both the endothelin and nitric oxide pathways with **1 tablet**[1]

Opsynvi®
macitentan/tadalafil
10 mg/40 mg tablets

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).**

Please read Important Safety Information throughout, and accompanying full Prescribing Information, including BOXED WARNING, for OPSYNVI®.

ERA=endothelin receptor antagonist; FDA=US Food and Drug Administration; PDE5i=phosphodiesterase type 5 inhibitor; WHO=World Health Organization.

OPSYNVI® Contains 2 Proven PAH Therapies in 1 Tablet[1,3,4]

For patients who are treatment naïve to any PAH therapy or transitioning from ERA monotherapy[1]

Starting dose:
1 OPSYNVI® 10 mg/20 mg tablet once daily
for 1 week

If tolerated, up-titrate to
1 OPSYNVI® 10 mg/40 mg tablet once daily

For patients who are transitioning from a stable-dose PDE5i monotherapy or ERA + PDE5i loose-dose combinations[1]

No titration needed

Start with
1 OPSYNVI® 10 mg/40 mg tablet once daily

1 once-daily tablet[1]

- OPSYNVI® (macitentan/tadalafil) can be administered with or without food
- Tablets should not be cut, crushed, or chewed
- If the patient misses a dose of OPSYNVI®, tell the patient to take it as soon as possible and then take the next dose at the regularly scheduled time. Tell the patient not to take 2 doses at the same time if a dose has been missed

Important information before starting treatment with OPSYNVI®

- Obtain a pregnancy test in females of reproductive potential prior to OPSYNVI® treatment, monthly during treatment, and one month after stopping OPSYNVI®. Initiate treatment with OPSYNVI® in females of reproductive potential only after a negative pregnancy test
- OPSYNVI® was not studied in patients undergoing dialysis. Avoid use of OPSYNVI® in patients with severe renal impairment
- OPSYNVI® was not studied in patients with severe hepatic impairment. OPSYNVI® must not be initiated in patients with severe hepatic impairment, or clinically significant elevated hepatic aminotransferases (>3 x ULN)

IMPORTANT SAFETY INFORMATION (continued)

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.

ULN=upper limit of normal.

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.

Drug Interactions With OPSYNVI®[1]

Opsynvi® macitentan/tadalafil 10 mg/40 mg tablets

Medication	Effect
Nitrates	• Administration of nitrates within 48 hours after the last dose of OPSYNVI® is contraindicated
Strong inducers of CYP3A4 (eg, rifampin)	• Significantly reduce macitentan exposure • Use of OPSYNVI® with strong CYP3A4 inducers should be avoided
Strong CYP3A4 inhibitors (eg, ketoconazole)	• Increase macitentan and tadalafil exposure • Concomitant use of OPSYNVI® with strong CYP3A4 inhibitors should be avoided • Use other PAH treatment options when strong CYP3A4 inhibitors are needed
Moderate dual or combined inhibitors of CYP3A4 and CYP2C9 (eg, fluconazole)	• Predicted to increase macitentan exposure 4-fold • Concomitant use of OPSYNVI® with moderate dual inhibitors of CYP3A4 and CYP2C9 should be avoided • Concomitant use of OPSYNVI® with both a moderate CYP3A4 inhibitor and moderate CYP2C9 inhibitor should also be avoided
Alpha-blockers	• PDE5 inhibitors, including tadalafil, and alpha-blockers are both vasodilators with blood pressure-lowering effects • Concomitant administration of alpha-blockers and tadalafil may lead to symptomatic hypotension • Combination of OPSYNVI® with doxazosin is not recommended
Antihypertensives	• PDE5 inhibitors, including tadalafil, are mild systemic vasodilators • In pharmacology studies, small reductions in blood pressure occurred following coadministration of tadalafil with selected antihypertensive medications* vs placebo
Alcohol	• Mild vasodilator, like tadalafil • When taken in combination, blood pressure-lowering effects of each individual compound may increase • Substantial consumption of alcohol (ie, ≥5 units) in combination with OPSYNVI® can increase the potential for orthostatic signs and symptoms, including heart rate, decrease in standing blood pressure, dizziness, and headache • Tadalafil (10 mg or 20 mg) did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations

The most common adverse reactions associated with OPSYNVI® are edema/fluid retention (21%), anemia (19%), and headache/migraine (18%). Discontinuations due to adverse events among patients receiving OPSYNVI® was 8%, most frequently due to anemia and hemoglobin decreased (2% grouped), and peripheral edema and peripheral swelling (2% grouped).[1]

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*Selected antihypertensive medications include amlodipine, angiotensin II receptor blockers, bendroflumethiazide, enalapril, and metoprolol.
CYP=cytochrome P450.

IMPORTANT SAFETY INFORMATION

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- **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®.

Important Safety Information

Opsynvi®
macitentan/tadalafil
10 mg/40 mg tablets

WARNINGS AND PRECAUTIONS (continued)

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 of the 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® to patients with PVOD, administration of OPSYNVI® to such patients is not recommended. Should signs of pulmonary edema occur when OPSYNVI® is 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.

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WARNINGS AND PRECAUTIONS (continued)

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® 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 and the concomitant administration of these agents may lead to symptomatic hypotension in some patients. 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.

Important Safety Information

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).

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cp-443044v1

References: 1. OPSYNVI® (macitentan/tadalafil) full Prescribing Information. Actelion Pharmaceuticals US, Inc. **2.** Grünig E, Jansa P, Fan F, et al. Randomized trial of macitentan/tadalafil single-tablet combination therapy for pulmonary arterial hypertension. *J Am Coll Cardiol*. 2024;83(4):473-484. **3.** Pulido T, Adzerikho I, Channick RN, et al; SERAPHIN Investigators. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369(9):809-818. doi:10.1056/NEJMoa1213917 **4.** Galiè N, Brundage BH, Ghofrani HA, et al; Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil therapy for pulmonary arterial hypertension. *Circulation*. 2009;119(22):2894-2903. doi:10.1161/CIRCULATIONAHA.108.839274

Summary

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Starting dose:
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If tolerated, up-titrate to
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For patients who are transitioning from a stable-dose PDE5i monotherapy or ERA + PDE5i loose-dose combinations[1]

No titration needed

Start with
1 OPSYNVI® 10 mg/40 mg tablet once daily

- The most common adverse reactions associated with OPSYNVI® are edema/fluid retention (21%), anemia (19%), and headache/migraine (18%)[1]
- Discontinuation due to adverse events among patients receiving OPSYNVI® was 8%[1]

Learn more at OPSYNVIhcp.com

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