OPSYNVI- macitentan and tadalafil tablet, film coated
Actelion Pharmaceuticals US, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OPSYNVI safely and effectively. See full prescribing information for OPSYNVI.

OPSYNVI ® (macitentan and tadalafil) tablets, for oral use
Initial U.S. Approval: 2024

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **Do not administer OPSYNVI to a pregnant female because it may cause fetal harm (4.1, 5.1, 8.1).**
- **Females of reproductive potential: exclude pregnancy before start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after treatment by using acceptable methods of contraception (2.2, 8.3).**
- **For all female patients, OPSYNVI is available only through a restricted program called the Macitentan-Containing Products Risk Evaluation and Mitigation Strategy (REMS) (5.2).**

INDICATIONS AND USAGE

OPSYNVI is a combination of macitentan, an endothelin receptor antagonist (ERA), and tadalafil, a phosphodiesterase 5 (PDE5) inhibitor, indicated for chronic treatment of pulmonary arterial hypertension (PAH, WHO Group I) in adult patients of WHO functional class (FC) II–III. (1.1)
Individually, macitentan reduces the risk of clinical worsening events and hospitalization, and tadalafil improves exercise ability. (1.1, 14)

DOSAGE AND ADMINISTRATION

- One 10 mg/20 mg or 10 mg/40 mg tablet taken orally once daily with or without food. (2.1)

DOSAGE FORMS AND STRENGTHS

Film-coated tablets:
- Macitentan 10 mg and tadalafil 20 mg (3)
- Macitentan 10 mg and tadalafil 40 mg (3)

CONTRAINDICATIONS

- Pregnancy (4.1)
- Hypersensitivity (4.2)
- Concomitant Organic Nitrates (4.3)
- Concomitant Guanylate Cyclase (GC) Stimulators (4.4)

WARNINGS AND PRECAUTIONS

- Hepatotoxicity: ERAs cause hepatotoxicity and liver failure. Obtain baseline liver enzymes and monitor as clinically indicated. (5.3)
- Hypotension: Vasodilatory effects may cause hypotension in susceptible patients. (5.4)
- Hemoglobin decrease. (5.5)
- Worsening Pulmonary Veno-Occlusive Disease: If pulmonary edema is confirmed, discontinue treatment. (5.6)
- Visual Loss: Sudden loss of vision could be a sign of non-arteritic ischemic optic neuropathy (NAION) and may be permanent. (5.7)
- Hearing Impairment: Cases of sudden decrease or loss of hearing have been reported in patients taking tadalafil. (5.8)
- Fluid Retention: Fluid retention may require intervention. (5.9)
- Combination with Other PDE5 Inhibitors: Avoid use with other PDE5 inhibitors. (5.10)
- Decreased Sperm Count: Decreases in sperm count have been observed in patients taking ERAs. (5.11)

- Prolonged Erection: Advise patients to seek emergency treatment if an erection lasts greater than 4 hours. (5.12)

ADVERSE REACTIONS

Most common adverse reactions (≥10%) are edema/fluid retention, anemia, and headache/migraine. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen at 1-800-526-7736 (1-800-JANSSEN) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- Strong CYP3A4 Inducers/Inhibitors: Avoid concomitant use (7.2, 7.3)
- Moderate Dual or Combined CYP3A4 and CYP2C9 Inhibitors: Avoid concomitant use (7.4)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed (8.2)
- Renal Impairment: Avoid use in patients with creatinine clearance 15–29 mL/min (8.6)
- Hepatic Impairment: Do not initiate in patients with severe hepatic impairment (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

- **Do not administer OPSYNVI to a pregnant female because it may cause fetal harm *[see Contraindications (4.1), Warnings and Precautions (5.1), and Use in Specific Populations (8.1)].***
- **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 *[see Use in Specific Populations (8.3)].***
- **For all female patients, OPSYNVI is available only through a restricted program called the Macitentan-Containing Products Risk Evaluation and Mitigation Strategy (REMS) *[see Warnings and Precautions (5.2)]*.**

1 INDICATIONS AND USAGE

1.1 Pulmonary Arterial Hypertension

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 *[see Clinical Studies (14.1)]* .

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

OPSYNVI is taken orally once daily with or without food. Swallow the tablets whole, with water. Do not cut, crush, or chew tablets. 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 two doses at the same time if a dose has been missed.

For patients who are treatment-naïve to any PAH specific therapy or transitioning from ERA monotherapy

The recommended starting dose of OPSYNVI is one 10 mg/20 mg tablet taken orally once daily with or without food for one week. If tolerated, up titrate OPSYNVI to one 10 mg/40 mg tablet taken orally once daily with or without food as the maintenance dose.

For patients transitioning from PDE5 inhibitor monotherapy or PDE5 inhibitor and ERA therapy in combination

The recommended dose of OPSYNVI is one 10 mg/40 mg tablet taken orally once daily.

2.2 Pregnancy Testing in Females of Reproductive Potential

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 *[see Contraindications (4.1), Warnings and Precautions (5.1), and Use in Specific Populations (8.3)].*

3 DOSAGE FORMS AND STRENGTHS

OPSYNVI is available as:

10 mg/20 mg	Pink	Oblong	Film-coated	"1020" on one side and "MT" on the other side
10 mg/40 mg	White to almost-white	Oblong	Film-coated	"1040" on one side and "MT" on the other side

4 CONTRAINDICATIONS

4.1 Pregnancy

OPSYNVI may cause fetal harm when administered to a pregnant woman. OPSYNVI is contraindicated in females who are pregnant. Macitentan was consistently shown to have teratogenic effects when administered to animals. If OPSYNVI is used during pregnancy, advise the patient of the potential risk to a fetus *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]* .

4.2 Hypersensitivity

OPSYNVI is contraindicated in patients with a history of a hypersensitivity reaction to macitentan, tadalafil, or any component of the product. Hypersensitivity reactions have been reported. Stevens-Johnson syndrome and exfoliative dermatitis have been reported with tadalafil *[see Adverse Reactions (6.2)].*

4.3 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. Tadalafil potentiates the hypotensive effect of nitrates. This potentiation is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway *[see Clinical Pharmacology (12.2)].*

4.4 Concomitant Guanylate Cyclase (GC) Stimulators

Coadministration of GC stimulators such as riociguat with OPSYNVI is contraindicated. Tadalafil may potentiate the hypotensive effects of GC stimulators.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-fetal Toxicity

OPSYNVI may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods and obtain monthly pregnancy tests *[see Dosage and Administration (2.2) and Use in Specific Populations (8.1, 8.3)].*

OPSYNVI is available for females through the Macitentan-Containing Products REMS, a restricted distribution program *[see Warnings and Precautions (5.2)]* .

5.2 Macitentan-Containing Products REMS

For all females, OPSYNVI is available only through a restricted program called the Macitentan-Containing Products REMS, because of the risk of embryo-fetal toxicity *[see Contraindications (4.1), Warnings and Precautions (5.1), and Use in Specific Populations (8.1, 8.3)]* .

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

- Prescribers must be certified with the Macitentan-Containing Products REMS by

enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Macitentan-Containing Products REMS 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 *[see Use in Specific Populations (8.3)]* .
- Pharmacies must be certified with the Macitentan-Containing Products REMS and must only dispense to patients who are authorized to receive OPSYNVI.

Further information is available at www.MacitentanREMS.com or 1-888-572-2934. Information on Macitentan-Containing Products REMS certified pharmacies or wholesale distributors is available at 1-888-572-2934.

5.3 Hepatotoxicity

ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure.

The incidence of elevated aminotransferases in the double-blind and combined double-blind (DB)/open-label (OL) arms of the study of OPSYNVI in PAH are shown in Table 1.

Table 1: Incidence of Elevated Aminotransferases in the A DUE Study

	OPSYNVI DB (N=107)	**OPSYNVI DB/OL (N=185)**
≥3 × ULN	1.0%	3.4%
≥8 × ULN	1.0%	1.1%

The overall incidence of treatment discontinuations for hepatic adverse events in the double-blind and combined double-blind/open-label arms study of OPSYNVI in PAH data were 0.9% and 2.2% respectively.

The incidence of elevated aminotransferases in the study of OPSUMIT (macitentan) in PAH is shown in Table 2.

Table 2: Incidence of Elevated Aminotransferases in the SERAPHIN Study

	OPSUMIT 10 mg (N=242)	**Placebo (N=249)**
>3 × ULN	3.4%	4.5%
>8 × ULN	2.1%	0.4%

In the placebo-controlled study of OPSUMIT, discontinuations for hepatic adverse events were 3.3% in the OPSUMIT 10 mg group vs. 1.6% for placebo.

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 × 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 × upper limit of normal [ULN]) at baseline. Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied, and, therefore, avoid use of OPSYNVI.

5.4 Hypotension

OPSYNVI tablets have vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing OPSYNVI tablets, carefully consider whether patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with pre-existing hypotension, with autonomic dysfunction, with left ventricular outflow obstruction, may be particularly sensitive to the actions of vasodilators *[see Clinical Pharmacology (12.2)].*

5.5 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 *[see Adverse Reactions (6.1)].*

5.6 Worsening Pulmonary Veno-Occlusive Disease (PVOD)

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with 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.

5.7 Visual Loss

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 PDE5 inhibitors, including tadalafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking. Based on published literature, the annual incidence of NAION is 2.5–11.8 cases per 100,000 in males aged greater than or

equal to 50 in the general population. Other risk factors for NAION, such as the presence of "crowded" optic disc, may have contributed to the occurrence of NAION.

Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use of OPSYNVI in these patients is not recommended.

5.8 Hearing Impairment

Cases of sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness, have been reported in patients taking tadalafil. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors.

5.9 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 active-controlled and combined double-blind/open-label arms of the 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 *[see Adverse Reactions (6.1)]* . In the placebo-controlled study of OPSUMIT in PAH, the incidence of edema was 21.9% in the OPSUMIT 10 mg group and 20.5% in the placebo group.

Patients with underlying left ventricular dysfunction may be at particular risk for developing significant fluid retention after initiation of ERA treatment. In a small study of OPSUMIT in patients with pulmonary hypertension because of left ventricular dysfunction, more patients in the OPSUMIT group developed significant fluid retention and had more hospitalizations because of worsening heart failure compared to those randomized to placebo. Postmarketing cases of edema and fluid retention occurring within weeks of starting OPSUMIT, some requiring intervention with a diuretic or hospitalization for decompensated heart failure, have been reported .

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.

5.10 Combination with Other PDE5 Inhibitors

Tadalafil is also indicated for erectile dysfunction. The safety and efficacy of taking tadalafil tablets together with another PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. Instruct patients taking OPSYNVI tablets not to take other PDE5 inhibitors.

5.11 Decreased Sperm Count

Macitentan, like other ERAs, may have an adverse effect on spermatogenesis. Counsel men about potential effects on fertility *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)].*

5.12 Prolonged Erection

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 (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease) are at an increased risk. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention.

6 ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Hypersensitivity *[see Contraindications (4.2)]*
- Embryo-fetal Toxicity *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Hypotension *[see Warnings and Precautions (5.4)]*
- Decrease in Hemoglobin *[see Warnings and Precautions (5.5)]*
- Visual Loss *[see Warnings and Precautions (5.7) and Patient Counseling Information (17)]*
- Hearing loss *[see Warnings and Precautions (5.8)]*
- Fluid Retention *[see Warnings and Precautions (5.9)]*
- Prolonged Erection *[see Warnings and Precautions (5.12)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The overall safety profile of OPSYNVI is based on data from a double-blind, active-controlled, phase 3 clinical study (A DUE) and an open-label extension study, in patients with PAH *[see Clinical Studies (14)]* . In the double-blind portion of the study, a total of 107 patients were treated with OPSYNVI 10 mg/40 mg, 35 patients were treated with 10 mg macitentan monotherapy, and 44 patients were treated with 40 mg tadalafil monotherapy. The duration of exposure to OPSYNVI during the double-blind portion was 16 weeks.

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). Table 3 presents adverse reactions seen in patients treated for 16 weeks during the double-blind portion of A DUE.

Table 3: Adverse Reactions Occurring in 3% or More of Patients Treated with OPSYNVI During the 16-week Double-blind Study Portion of A DUE

Adverse	OPSYNVI	Macitentan Monotherapy	Tadalafil Monotherapy

Adverse Reaction	N=107 %	Monotherapy N=35 %	Monotherapy N=44 %
Edema/fluid retention	21	14	16
Anemia	19	3	2
Headache	18	17	14
Abdominal pain	7	3	14
Hypotension	7	0	0
Myalgia	6	0	5
Nasopharyngitis	6	3	0
Nausea	6	0	7
Increased uterine bleeding	5	0	0
Back pain	5	3	9
Flushing	4	6	0
Vomiting	4	0	5
Palpitations	4	3	5
Pain in extremity	3	0	7
Epistaxis	3	0	0

One-hundred eighty-five patients received OPSYNVI in the double-blind or open-label phase of the study. The median exposure to OPSYNVI during the combined double-blind/open-label extension was 59.9 weeks with a mean exposure of 63.2 weeks. Adverse reactions from the combined double-blind/open-label study data were similar to those observed in the double-blind study.

The following adverse reactions have been reported during clinical trials with the individual components of OPSYNVI but were not observed in 3% or more of subjects treated with OPSYNVI in the A DUE clinical trial:

Macitentan: bronchitis, pharyngitis, transaminases increased, influenza, urinary tract infection.

Tadalafil: lower respiratory tract infection, prolonged erections, gastroesophageal reflux disease, vision blurred, tinnitus, swelling face, chest pain.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during post-approval use of tadalafil. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Macitentan: liver injury, symptomatic hypotension, hypersensitivity reactions (angioedema, pruritus, and rash).

Tadalafil: Cardiovascular and cerebrovascular events including myocardial infarction, sudden cardiac death, stroke, and tachycardia; Nervous system events including, seizure, transient amnesia; Hypersensitivity reactions including urticaria, Stevens-Johnson syndrome, and exfoliative dermatitis; visual field defect, NAION, retinal vascular

occlusion; sudden hearing loss, priapism.

7 DRUG INTERACTIONS

7.1 Nitrates

Administration of nitrates within 48 hours after the last dose of OPSYNVI is contraindicated *[see Contraindications (4.3)]* .

7.2 Strong CYP3A4 Inducers

Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Use of OPSYNVI with strong CYP3A4 inducers should be avoided *[see Clinical Pharmacology (12.3)].*

7.3 Strong CYP3A4 Inhibitors

Concomitant use of strong CYP3A4 inhibitors like ketoconazole increase 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 *[see Clinical Pharmacology (12.3)].*

7.4 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) *[see Clinical Pharmacology (12.3)].*

Concomitant treatment of both a moderate CYP3A4 inhibitor and moderate CYP2C9 inhibitor with OPSYNVI should also be avoided *[see Clinical Pharmacology (12.3)].*

7.5 Alpha-Blockers

PDE5 inhibitors, including tadalafil, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. In patients who are taking alpha $_1$ blockers, concomitant administration of tadalafil may lead to symptomatic hypotension in some patients. Therefore, the combination of OPSYNVI and doxazosin is not recommended *[see Warnings and Precautions (5.4) and Clinical Pharmacology (12.2)].*

7.6 Antihypertensives

PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood–pressure–lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendroflumethiazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo *[see Clinical Pharmacology (12.2)].*

7.7 Alcohol

Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure–lowering effects of each individual

compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) 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. Tadalafil (10 mg or 20 mg) did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations *[see Clinical Pharmacology (12.2)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on data from animal reproduction studies, 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. The available data from OPSYNVI pharmacovigilance reports and published case reports on macitentan are insufficient to evaluate the potential risk of embryo-fetal toxicity. Macitentan was teratogenic in rabbits and rats at all doses tested.

Available data from a randomized controlled trial, observational studies, and case series with tadalafil use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In tadalafil animal reproduction studies, no adverse developmental effects were observed with oral administration of tadalafil to pregnant rats and mice during organogenesis at exposures 7 times the maximum recommended human dose (MRHD) of 40 mg/day *(see Data)* .

There are risks to the mother and the fetus associated with PAH in pregnancy *(see Clinical Considerations)* . If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise pregnant women of the potential risk to a fetus *[see Contraindications (4.1) and Warnings and Precautions (5.1)].*

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo/Fetal Risk

In patients with PAH, pregnancy is associated with an increased rate of maternal and fetal morbidity and mortality, including heart failure, stroke, spontaneous abortion, intrauterine growth restriction, premature labor, and preterm birth.

Data

Animal Data

Macitentan

In both rabbits and rats, there were cardiovascular and mandibular arch fusion abnormalities. Administration of macitentan to female rats from late pregnancy through lactation caused reduced pup survival and impairment of the male fertility of the

offspring at all dose levels tested.

Tadalafil

Tadalafil and/or its metabolites cross the placenta, resulting in fetal exposure in rats.

Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at unbound tadalafil exposures up to 7 times the exposure at the maximum recommended human dose (MRHD) of 40 mg/day during organogenesis based on AUC. In one of two perinatal/postnatal developmental studies in rats, a reduction of postnatal pup survival was observed at dose levels of 60, 200 and 1000 mg/kg. The no-observed-effect-level (NOEL) for developmental toxicity was 30 mg/kg, which provided maternal exposure to unbound tadalafil concentrations approximately 5 times the exposure at the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 200 mg/kg/day, which produced AUCs greater than 8 times the exposure at the MRHD. Surviving offspring had normal development and reproductive performance.

8.2 Lactation

Risk Summary

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. Tadalafil and/or its metabolites are present in the milk of lactating rats *(see Data)* . When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in breastfed infants from OPSYNVI, advise women not to breastfeed during treatment with OPSYNVI.

Data

Tadalafil and/or its metabolites are present in the milk of lactating rats at concentrations approximately 2.4-times that found in the plasma.

8.3 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 *[see Dosage and Administration (2.2) and Contraindications (4.1)].*

Contraception

Female patients of reproductive potential must use acceptable methods of contraception during treatment with OPSYNVI and for 1 month after treatment with OPSYNVI. Patients may 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). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider

trained in contraceptive counseling *[see Warnings and Precautions (5.1)]* .

Infertility

Males

Macitentan

Based on findings in animals, macitentan may impair fertility in males of reproductive potential. It is not known whether effects on fertility would be reversible *[see Warnings and Precautions (5.11), Clinical Pharmacology (12.2), and Nonclinical Toxicology (13.1)].*

Tadalafil

Based on the data from 3 studies in adult males, tadalafil decreased sperm concentrations in the study of 10 mg tadalafil for 6 months and the study of 20 mg tadalafil for 9 months. This effect was not seen in the study of 20 mg tadalafil taken for 6 months. There was no adverse effect of tadalafil 10 mg or 20 mg on mean concentrations of testosterone, luteinizing hormone or follicle stimulating hormone. The clinical significance of the decreased sperm concentrations in the two studies is unknown. There have been no studies evaluating the effect of tadalafil on fertility in men or women *[see Clinical Pharmacology (12.2) and Nonclinical Toxicology (13.1)]* .

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the total number of subjects in the clinical study of OPSYNVI for PAH, 20% were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

8.6 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) because of increased tadalafil exposure (AUC), lack of clinical experience and the lack of ability to influence clearance by dialysis. For patients with mild (creatinine clearance 51–80 mL/min) to moderate (creatinine clearance 30–50 mL/min) renal impairment, the recommended dose should be consistent with the adult dosing *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)].*

8.7 Hepatic Impairment

OPSYNVI was not studied in severe hepatic impairment patients defined as a Model for End-Stage Liver Disease score ≥19. OPSYNVI must not be initiated in patients with severe hepatic impairment, or clinically significant elevated hepatic aminotransferases (greater than 3 times the Upper Limit of Normal at baseline (> 3 × ULN). For patients with mild to moderate hepatic impairment (Child Pugh Class A or B) the recommended dose should be consistent with the adult dosing see *Dosage and Administration (2.1) [see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)].*

10 OVERDOSAGE

In the event of an overdose, standard supportive measures should be taken, as required. Dialysis is unlikely to be effective because macitentan is highly protein-bound.

Macitentan

Macitentan has been administered as a single dose of up to and including 600 mg to healthy subjects (60 times the approved dosage). Adverse reactions of headache, nausea and vomiting were observed.

Tadalafil

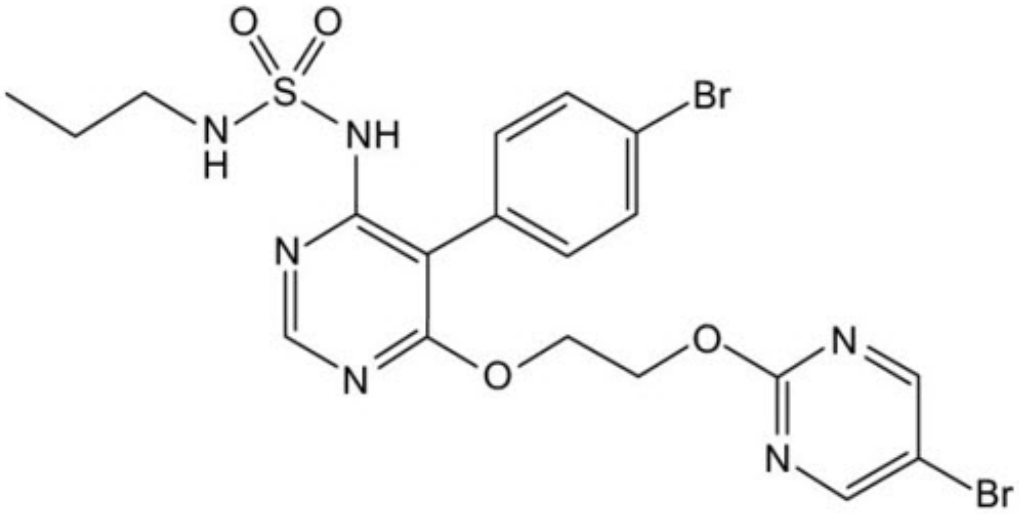
Single doses of tadalafil up to 500 mg have been given to healthy male subjects, and multiple daily doses up to 100 mg have been given to male patients with erectile dysfunction. Adverse reactions were similar to those seen at lower doses. Doses greater than 40 mg have not been studied in patients with PAH. Hemodialysis contributes negligibly to tadalafil elimination.

11 DESCRIPTION

OPSYNVI ®is a single tablet combination containing two oral components used to treat pulmonary arterial hypertension: macitentan, an endothelin receptor antagonist (ERA), and tadalafil, a phosphodiesterase 5 (PDE5) inhibitor.

Macitentan

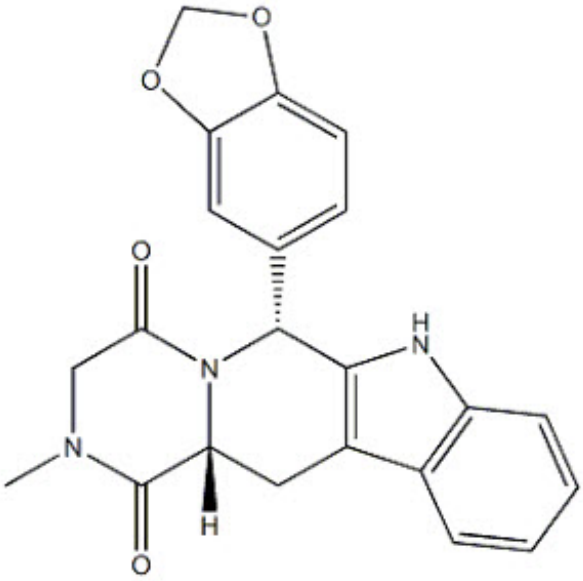
Macitentan is an endothelin receptor antagonist. The chemical name of macitentan is N-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4- pyrimidinyl]-N'-propylsulfamide. It has a molecular formula of $C_{19}H_{20}Br_2N_6O_4S$ and a molecular weight of 588.27. Macitentan is achiral and has the following structural formula:



Macitentan is a crystalline powder that is insoluble in water. In the solid state macitentan is very stable, is not hygroscopic, and is not light sensitive.

Tadalafil

Tadalafil, an oral treatment for pulmonary arterial hypertension, is a selective inhibitor of cyclic guanosine monophosphate (cGMP)–specific phosphodiesterase type 5 (PDE5). Tadalafil has the empirical formula $C_{22}H_{19}N_3O_4$ representing a molecular weight of 389.41. The structural formula is:



The chemical designation is pyrazino[1´,2´:1,6]pyrido[3,4–b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-. It is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol.

OPSYNVI

OPSYNVI is available as 10 mg/20 mg macitentan/tadalafil and 10 mg/40 mg macitentan/tadalafil film-coated tablets for oral administration.

Each OPSYNVI core tablet contains the following inactive ingredients: Hydroxypropyl cellulose, hydroxypropyl cellulose (low-substituted), lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate 80, povidone, sodium starch glycolate, sodium lauryl sulfate.

OPSYNVI 10 mg/20 mg tablets are film-coated with a coating material containing hydroxypropyl methylcellulose, iron oxide red, iron oxide yellow, lactose monohydrate, talc, titanium dioxide, and triacetin.

OPSYNVI 10 mg/40 mg tablets are film-coated with a coating material containing hydroxypropyl methylcellulose, lactose monohydrate, talc, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Macitentan

Endothelin (ET)-1 and its receptors (ETA and ETB) mediate a variety of deleterious effects, such as vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation. In disease conditions such as PAH, the local ET system is upregulated and is involved in vascular hypertrophy and in organ damage.

Macitentan is an endothelin receptor antagonist that inhibits the binding of ET-1 to both ETA and ETB receptors. Macitentan displays high affinity and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells. One of the metabolites of macitentan is also pharmacologically active at the ET receptors and is estimated to be

about 20% as potent as the parent drug *in vitro*. The clinical impact of dual endothelin blockage is unknown.

Tadalafil

Tadalafil is an inhibitor of phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). PAH is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations in the pulmonary vascular smooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by tadalafil increases the concentrations of cGMP resulting in relaxation of pulmonary vascular smooth muscle cells and vasodilation of the pulmonary vascular bed.

Studies *in vitro* have shown that tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in corpus cavernosum, vascular smooth muscle, visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum. The effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. Tadalafil is > 10,000-fold more potent for PDE5 than for PDE1, PDE2, PDE4 and PDE7, enzymes which are found in the heart, brain, blood vessels, liver, and other organs. Tadalafil is > 10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. This selectivity for PDE5 over PDE3 is important because PDE3 is an enzyme involved in cardiac contractility. Additionally, tadalafil is approximately 700-fold more potent for PDE5 than for PDE6, an enzyme which is found in the retina and is responsible for phototransduction. Tadalafil is also > 9,000-fold more potent for PDE5 than for PDE8, PDE9 and PDE10.

12.2 Pharmacodynamics

Pharmacodynamic studies with OPSYNVI have not been conducted. As OPSYNVI contains macitentan and tadalafil, the pharmacodynamic effects for each component should be considered.

Pulmonary Hemodynamics of Macitentan

The SERAPHIN clinical efficacy study in patients with PAH assessed hemodynamic parameters in a subset of patients after 6 months of treatment. Patients treated with macitentan 10 mg (N=57) achieved a median reduction of 37% (95% CI 22–49) in pulmonary vascular resistance and an increase of 0.6 L/min/m ^{2} (95% CI 0.3–0.9) in cardiac index compared to placebo (N=67).

Effects on Cardiac Electrophysiology

Macitentan

In a randomized, placebo-controlled four-way crossover study with a positive control in healthy subjects, repeated doses of macitentan 10 and 30 mg (3 times the recommended dosage) had no significant effect on the QTc interval.

Tadalafil

In a randomized, placebo-controlled four-way crossover study with a positive control in healthy subjects, a single dose of 100 mg tadalafil (2.5 times the recommended dosage) had no significant effect on the QTc interval.

Effects on Blood Pressure When Administered with Nitrates

In clinical pharmacology studies, tadalafil (5 to 20 mg) was shown to potentiate the hypotensive effect of nitrates. Do not use OPSYNVI in patients taking any form of nitrates *[see Contraindications (4.3)].*

A double–blind, placebo–controlled, crossover study in 150 male subjects at least 40 years of age (including subjects with diabetes mellitus and/or controlled hypertension) assessed the interaction between nitroglycerin and tadalafil. Subjects received daily doses of tadalafil 20 mg or matching placebo for 7 days and then were given a single dose of 0.4 mg sublingual nitroglycerin (NTG) at pre–specified timepoints following their last dose of tadalafil (2, 4, 8, 24, 48, 72, and 96 hours after tadalafil). A significant interaction between tadalafil and NTG was observed at each timepoint up to and including 24 hours. At 48 hours, by most hemodynamic measures, the interaction between tadalafil and NTG was not observed, although a few more tadalafil subjects compared to placebo experienced greater blood-pressure-lowering effects at this timepoint. After 48 hours, the interaction was not detectable *[see Contraindications (4.3)].*

Effects on Vision

Single oral doses of PDE inhibitors have demonstrated transient dose-related impairment of color discrimination (blue/green), using the Farnsworth–Munsell 100–hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. In a study to assess the effects of a single dose of tadalafil 40 mg on vision (N=59), no effects were observed on visual acuity, intraocular pressure, or pupillometry. Across all clinical studies with tadalafil, reports of changes in color vision were rare (<0.1% of patients).

Dose-Response Relationship

Dose-response relationships, between 20 mg and 40 mg of tadalafil, were not observed for 6-minute walk distance or pulmonary vascular resistance (PVR) in subjects with PAH in the placebo-controlled study. Median change from baseline in 6-minute walk distance was 32 meters and 35 meters at 16 weeks in subjects receiving 20 mg and 40 mg daily, respectively. Mean change from baseline PVR was -254 dynes*sec*cm and -209 dynes*sec*cm at 16 weeks in patients receiving 20 mg and 40 mg daily, respectively.

12.3 Pharmacokinetics

Macitentan

The pharmacokinetics of macitentan and its active metabolite have been studied primarily in healthy subjects. The pharmacokinetics of macitentan are dose proportional over a range from 1 mg to 30 mg after once daily administration.

A cross study comparison shows that the exposures to macitentan and its active metabolite in patients with PAH are similar to those observed in healthy subjects.

Tadalafil

Over a dose range of 2.5 to 20 mg, tadalafil exposure (AUC) increases proportionally with dose in healthy subjects. In PAH patients administered between 20 and 40 mg of tadalafil, an approximately 50% greater AUC was observed indicating a less than proportional increase in exposure over the entire dose range of 2.5 to 40 mg.

During tadalafil 20 and 40 mg once daily dosing, steady-state plasma concentrations

were attained within 5 days, and exposure was approximately 30% higher than after a single dose.

Absorption

Macitentan

After a single oral administration of OPSYNVI, the maximum plasma concentration of macitentan is achieved in about 10 hours. The absolute bioavailability after oral administration is not known. In a study in healthy subjects, the exposure to macitentan and its active metabolite were unchanged after a high fat breakfast. OPSYNVI may therefore be taken with or without food.

Tadalafil

After a single oral-dose administration of OPSYNVI, the maximum observed plasma concentration (C_{max}) of tadalafil is achieved in about 3 hours. Absolute bioavailability of tadalafil following oral dosing has not been determined. Food intake does not significantly alter the rate and extent of absorption of tadalafil and OPSYNVI may be taken with or without food.

Distribution

Macitentan

Macitentan and its active metabolite are highly bound to plasma proteins (>99%), primarily to albumin and to a lesser extent to alpha-1-acid glycoprotein. The apparent volumes of distribution (Vss/F) of macitentan and its active metabolite were about 50 L and 40 L respectively in healthy subjects.

Tadalafil

The mean apparent volume of distribution following oral administration is approximately 77 L, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins.

Metabolism

Macitentan

Following oral administration, the apparent elimination half-lives of macitentan and its active metabolite are approximately 16 and 48 hours, respectively. Macitentan is metabolized primarily by oxidative depropylation of the sulfamide to form the pharmacologically active metabolite. This reaction is dependent on the cytochrome P450 (CYP) system, mainly CYP3A4 with minor contributions of CYP2C8, CYP2C9, and CYP2C19. At steady state in PAH patients, the systemic exposure to the active metabolite is 3-times the exposure to macitentan and is expected to contribute approximately 40% of the total pharmacologic activity.

Tadalafil

Tadalafil is predominantly metabolized by CYP3A to a catechol metabolite. The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatechol and methylcatechol glucuronide conjugate, respectively. The major circulating metabolite is the methylcatechol glucuronide. Methylcatechol concentrations are less than 10% of glucuronide concentrations. *In vitro* data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations.

Elimination

Macitentan

In a study in healthy subjects with radiolabeled macitentan, approximately 50% of radioactive drug material was eliminated in urine but none was in the form of unchanged drug or the active metabolite. About 24% of the radioactive drug material was recovered from feces.

Tadalafil

Following 40 mg, the mean oral clearance for tadalafil is 3.4 L/hr and the mean effective half-life is 11 hours in healthy subjects. In patients with pulmonary hypertension not receiving concomitant bosentan, the mean oral clearance for tadalafil is 1.6 L/hr. Tadalafil is excreted predominantly as metabolites, mainly in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

Population Pharmacokinetics

Tadalafil

In patients with pulmonary hypertension not receiving concomitant bosentan, the average tadalafil exposure at steady-state following 40 mg was 26% higher when compared to those of healthy volunteers. The results suggest a lower clearance of tadalafil in patients with pulmonary hypertension compared to healthy volunteers.

Specific Populations

Renal Impairment

Macitentan

Exposure to macitentan and its active metabolite in patients with severe renal impairment (creatinine clearance 15–29 mL/min) compared to healthy subjects was increased by 30% and 60%, respectively. This increase is not considered clinically relevant.

Tadalafil

In clinical pharmacology studies using single-dose tadalafil (5 to 10 mg), tadalafil exposure (AUC) doubled in subjects with mild (creatinine clearance 51 to 80 mL/min) or moderate (creatinine clearance 30 to 50 mL/min) renal impairment. In subjects with end-stage renal disease on hemodialysis, C_{max} doubled and AUC was 2.7 to 4.1 times as high following single-dose administration of 10 or 20 mg tadalafil, respectively. Exposure to total methylcatechol (unconjugated plus glucuronide) was 2 to 4-times as high in subjects with renal impairment, compared to those with normal renal function. Hemodialysis (performed between 24-and 30-hours post-dose) contributed negligibly to tadalafil or metabolite elimination.

Hepatic Impairment

Macitentan

Exposure to macitentan was decreased by 21%, 34%, and 6% and exposure to the active metabolite was decreased by 20%, 25%, and 25% in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, and C), respectively. This decrease is not considered clinically relevant.

Tadalafil

In clinical pharmacology studies, tadalafil exposure (AUC) in subjects with mild or moderate hepatic impairment (Child-Pugh Class A or B) was similar to exposure in healthy subjects when a dose of 10 mg was administered. There are no available data for doses higher than 10 mg of tadalafil in patients with hepatic impairment. Insufficient data are available for subjects with severe hepatic impairment (Child-Pugh Class C) .

Geriatric Patients

Macitentan

There are no clinically relevant effects of age on the pharmacokinetics of macitentan and its active metabolite.

Tadalafil

In healthy male elderly subjects (65 years or over) after a 10 mg dose, a lower oral clearance of tadalafil, resulting in 25% higher exposure (AUC) with no effect on C_{max} was observed relative to that in healthy subjects 19 to 45 years of age.

Patients with Diabetes Mellitus

Tadalafil

In male patients with diabetes mellitus after a 10 mg tadalafil dose, exposure (AUC) was reduced approximately 19% and C_{max} was 5% lower than that observed in healthy subjects. No dose adjustment is warranted.

Race and gender

There are no clinically relevant effects of race or gender on macitentan, its active metabolite, or tadalafil.

Drug Interactions

No clinical study evaluating drug interactions has been performed using OPSYNVI. Interactions that have been identified in studies with individual components of OPSYNVI (macitentan or tadalafil) determine the interactions that may occur with OPSYNVI. Co-administration of macitentan (10 mg once daily) and tadalafil (40 mg once daily) had no clinically relevant effect on the pharmacokinetics of either macitentan or tadalafil.

Macitentan

The metabolism of macitentan to its active metabolite is catalyzed mainly by CYP3A4, with minor contributions from CYP2C8, CYP2C9, and CYP2C19.

Macitentan and its active metabolite do not have relevant inhibitory or inducing effects on CYP enzymes.

Macitentan and its active metabolite are not substrates of the multi-drug resistance protein (P-gp, MDR-1) or organic anion transporting polypeptides (OATP1B1 and OATP1B3).

Macitentan and its active metabolite are not inhibitors of hepatic or renal drug transporters at clinically relevant concentrations.

Tadalafil

Tadalafil is a substrate of and predominantly metabolized by CYP3A.

Effects of other drugs on macitentan or tadalafil

Strong CYP3A4 inducers or inhibitors

Macitentan

Concomitant treatment with rifampicin 600 mg daily, a potent inducer of CYP3A4, reduced the steady-state exposure to macitentan by 79% but did not affect the exposure to the active metabolite *[see Drug Interactions (7.2)].*

Concomitant use of strong CYP3A4 inhibitors like ketoconazole approximately double macitentan exposure. Effects of other strong CYP3A4 inhibitors such as ritonavir on macitentan were not studied but are likely to result in an increase in macitentan exposure at steady state similar to that seen with ketoconazole *[see Drug Interactions (7.3)]* .

A moderate dual inhibitor of CYP3A4 and CYP2C9 such as fluconazole (400 mg once daily) is predicted to increase macitentan exposure approximately 4-fold without relevant effect on the exposure to its active metabolite *[see Drug Interactions (7.4)]* .

Tadalafil

Rifampin (600 mg daily), a CYP3A inducer, reduced tadalafil 10 mg single-dose exposure (AUC) by 88% and C_{max} by 46%, relative to the values for tadalafil 10 mg alone *[see Drug Interactions (7.2)]* .

Bosentan, a substrate of CYP2C9 and CYP3A and a moderate inducer of CYP3A, CYP2C9 and possibly CYP2C19, reduced tadalafil systemic exposure following multiple-dose coadministration. Although specific interactions have not been studied, other CYP3A inducers, such as carbamazepine, phenytoin, and phenobarbital, would likely decrease tadalafil exposure *[see Drug Interactions (7.2)].*

Ketoconazole increased tadalafil exposure relative to the values for tadalafil alone. Although specific interactions have not been studied, other CYP3A inhibitors, such as erythromycin, itraconazole, and grapefruit juice, would likely increase tadalafil exposure *[see Drug Interactions (7.3)].*

Ritonavir increased tadalafil 20-mg single-dose exposure relative to the values for tadalafil alone. Ritonavir inhibits and induces CYP3A, the enzyme involved in the metabolism of tadalafil, in a time-dependent manner. The initial inhibitory effect of ritonavir on CYP3A may be mitigated by a more slowly evolving induction effect so that after about 1 week of ritonavir twice daily, the exposure of tadalafil is similar in the presence of and absence of ritonavir *[see Drug Interactions (7.3)]* .

Effects of macitentan or tadalafil on other medicinal products

Macitentan

Macitentan once daily dosing did not alter the exposure to R- and S-warfarin or their effect on international normalized ratio (INR).

At steady state, the exposure to sildenafil 20 mg t.i.d. increased by 15% during concomitant administration of macitentan 10 mg once daily. This change is not considered clinically relevant. Macitentan 10 mg once daily did not affect the pharmacokinetics of an oral contraceptive (norethisterone 1 mg and ethinyl estradiol 35 µg).

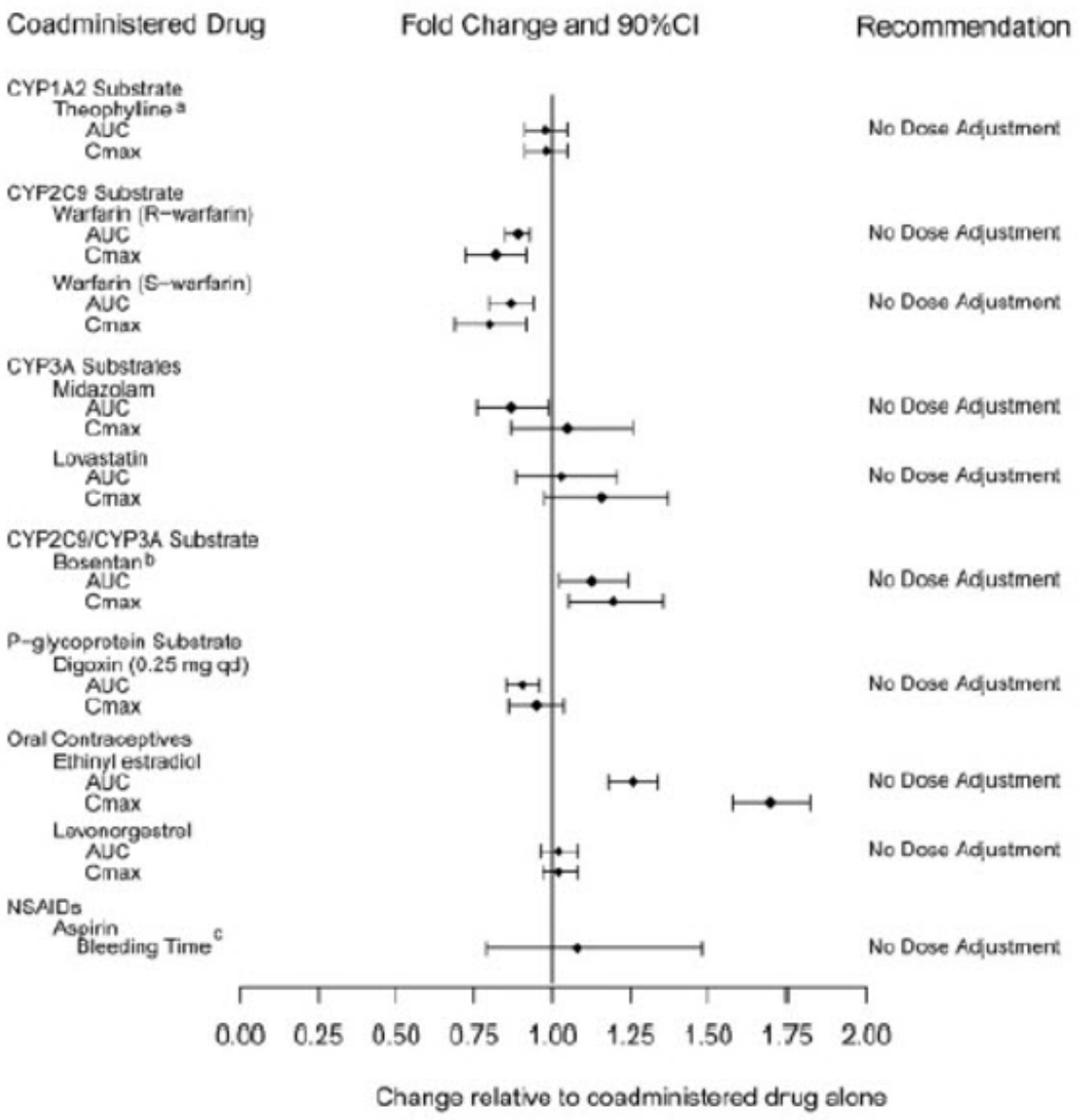
Macitentan 10 mg once daily did not affect the pharmacokinetics of concomitant use of a BCRP substrate drug (riociguat 1 mg and rosuvastatin 10 mg).

Tadalafil

Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms.

Exposure changes of drugs following co-administration with tadalafil are shown in Figure 1.

Figure 1: Impact of Tadalafil on the Pharmacokinetics of Other Drugs



[a] A small augmentation (increase of 3 beats per minute) in heart rate was observed with theophylline.
[b] Tadalafil (40 mg qd) had no clinically significant effect on exposure (AUC and C) of bosentan
metabolites.
[c] 95% CI

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Macitentan

Carcinogenicity studies of 2 years' duration did not reveal any carcinogenic potential at exposures 75-fold and 140-fold the human exposure (based on AUC) in male and female mice, respectively, and 8.3-and 42-fold in male and female rats, respectively.

Tadalafil

Tadalafil was not carcinogenic to rats or mice when administered daily for 2 years at doses up to 400 mg/kg/day. Systemic drug exposures, as measured by AUC of unbound tadalafil, were approximately 5-fold for mice, and 7-and 14-fold for male and female rats, respectively, the exposures at the maximum recommended human dose (MRHD) of 40 mg.

Mutagenesis

Macitentan

Macitentan was not genotoxic in a standard battery of *in vitro* and *in vivo* assays that included a bacterial reverse mutation assay, an assay for gene mutations in mouse lymphoma cells, a chromosome aberration test in human lymphocytes, and an *in vivo* micronucleus test in rats.

Tadalafil

Tadalafil was not mutagenic in the *in vitro* bacterial Ames assays or the forward mutation test in mouse lymphoma cells. Tadalafil was not clastogenic in the *in vitro* chromosomal aberration test in human lymphocytes or the *in vivo* rat micronucleus assays.

Impairment of Fertility

Macitentan

Treatment of juvenile rats from postnatal Day 4 to Day 114 led to reduced body weight gain and testicular tubular atrophy at exposures 7-fold the human exposure. Fertility was not affected.

Reversible testicular tubular dilatation was observed in chronic toxicity studies at exposures greater than 7-fold and 23-fold the human exposure in rats and dogs, respectively. After 2 years of treatment, tubular atrophy was seen in rats at 4-fold the human exposure. Macitentan did not affect male or female fertility at exposures ranging from 19-to 44-fold the human exposure, respectively, and had no effect on sperm count, motility, and morphology in male rats. No testicular findings were noted in mice after treatment up to 2 years.

Tadalafil

There were no effects on fertility, reproductive performance or reproductive organ morphology in male or female rats given oral doses of tadalafil up to 400 mg/kg/day, a dose producing AUCs for unbound tadalafil of 6-fold for males or 17-fold for females the exposures at the MRHD of 40 mg. In beagle dogs given tadalafil daily for 3 to 12 months, there was treatment-related non-reversible degeneration and atrophy of the

seminiferous tubular epithelium in the testes in 20–100% of the dogs that resulted in a decrease in spermatogenesis in 40–75% of the dogs at doses of ≥10 mg/kg/day. Systemic exposure (based on AUC) at no-observed-adverse-effect-level (NOAEL) (10 mg/kg/day) for unbound tadalafil was similar to that expected in humans at the MRHD of 40 mg.

There were no treatment-related testicular findings in rats or mice treated with doses up to 400 mg/kg/day for 2 years.

13.2 Animal Toxicology and/or Pharmacology

Macitentan

In dogs, macitentan decreased blood pressure at exposures similar to the therapeutic human exposure. Intimal thickening of coronary arteries was observed at 17-fold the human exposure after 4 to 39 weeks of treatment. Due to the species-specific sensitivity and the safety margin, this finding is considered not relevant for humans.

There were no adverse liver findings in long-term studies conducted in mice, rats and dogs at exposures of 12-to 116-fold the human exposure.

Tadalafil

Animal studies showed vascular inflammation in tadalafil-treated mice, rats, and dogs. In mice and rats, lymphoid necrosis and hemorrhage were seen in the spleen, thymus, and mesenteric lymph nodes at unbound tadalafil exposure of 1-to 17-fold the human exposure (AUCs) at the MRHD of 40 mg. In dogs, an increased incidence of disseminated arteritis was observed in 1-and 6-month studies at unbound tadalafil exposure of 0.5-to 38-fold the human exposure (AUC) at the MRHD of 40 mg. In a 12-month dog study, no disseminated arteritis was observed, but 2 dogs exhibited marked decreases in white blood cells (neutrophils) and moderate decreases in platelets with inflammatory signs at unbound tadalafil exposures of approximately 4-to 10-fold the human exposure at the MRHD of 40 mg. The abnormal blood-cell findings were reversible within 2 weeks upon removal of the drug.

14 CLINICAL STUDIES

14.1 Pulmonary Arterial Hypertension

OPSYNVI

OPSYNVI was demonstrated to reduce pulmonary vascular resistance (PVR) in a multi-national, multi-center, double-blind, adaptive, randomized, active-controlled, parallel-group study [NCT03904693 (A DUE)] in 187 patients with PAH (WHO FC II–III). The study was designed to compare the efficacy and safety of OPSYNVI to each monotherapy macitentan or tadalafil. Patients with PVR of at least 240 dyn•s/cm ^{5} were randomized to receive OPSYNVI (n=108), 10 mg macitentan monotherapy (n=35) or 40 mg tadalafil monotherapy (n=44), once daily.

Patients who received treatment during the double-blind treatment period (n=186) were either treatment-naïve (53%) or on an ERA (17%) or a PDE5 inhibitor (30%). Patients enrolled had idiopathic PAH (51%), heritable PAH (5%), PAH associated with connective tissue disease (35%), or PAH associated with congenital heart disease (3%). The mean

age was 50 years (range 18–80), 20% of patients were ≥65 years of age, 22% were male and 62% were white. At the time of enrollment, 51% of patients were WHO FC II and 49% were WHO FC III.

Patients who were not on a therapeutic PDE5 inhibitor dose at baseline received a 1-week titration period of macitentan 10 mg and tadalafil 20 mg.

The primary endpoint of the study was change from baseline in PVR (expressed as the ratio of geometric means of end of double-blind treatment to baseline) vs the individual component monotherapies after 16 weeks.

Hemodynamic

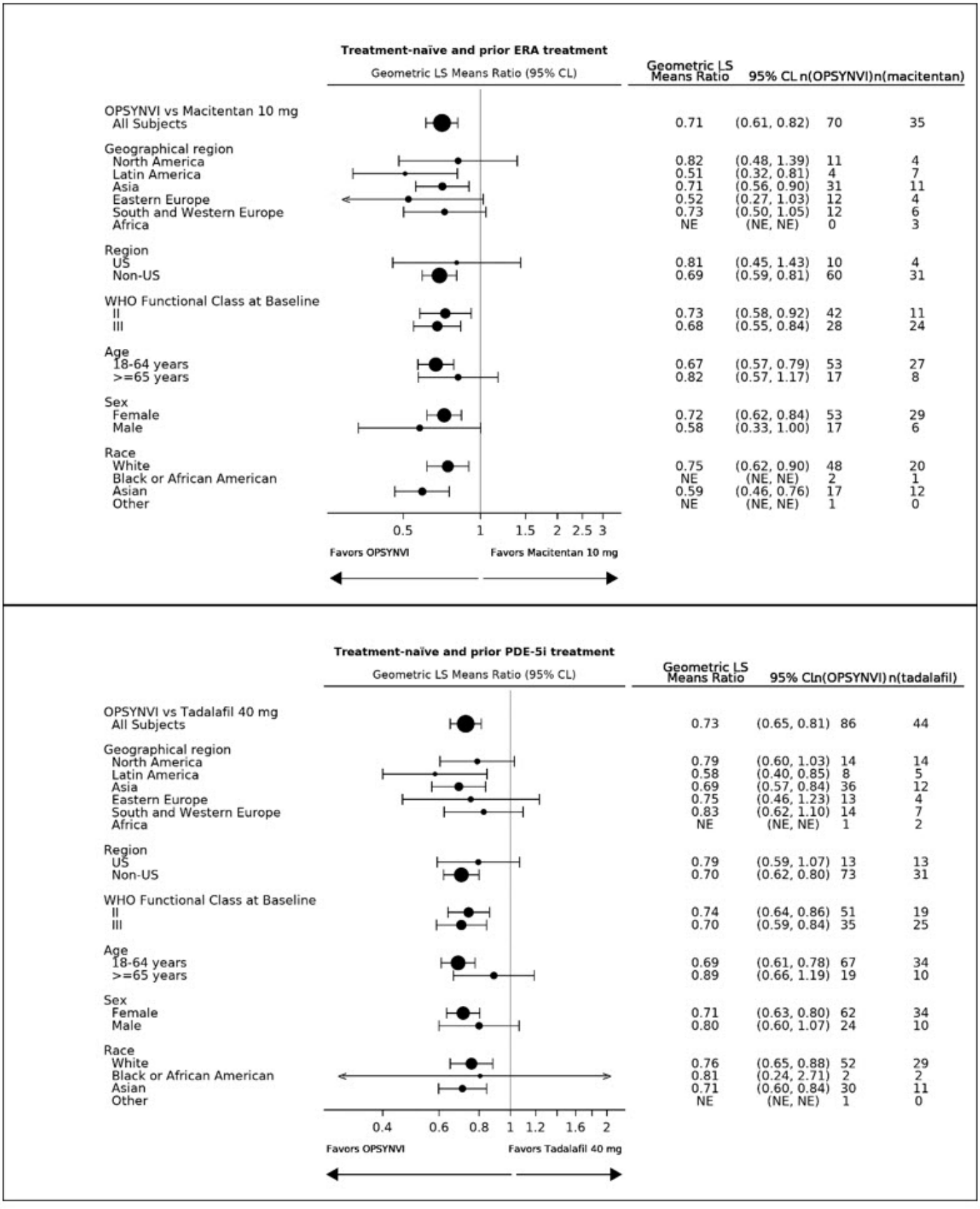
OPSYNVI demonstrated greater reduction in PVR after 16 weeks. Treatment with OPSYNVI resulted in a statistically significant treatment effect of 0.71 (95% CL 0.61, 0.82, $p < 0.0001$) representing a 29% reduction in PVR as compared to macitentan, and of 0.72 (95% CLs 0.64, 0.80, $p < 0.0001$) representing a 28% reduction in PVR as compared to tadalafil (Table 4).

Table 4: Change from Baseline in PVR at Week 16

	Treatment-naïve and Prior ERA Treatment		**Treatment-naïve and Prior PDE5 Inhibitor Treatment**	
	Macitentan (n=35)	**OPSYNVI (n=70)**	**Tadalafil (n=44)**	**OPSYNVI (n=86)**
Baseline mean (SD)	816 (401)	834 (631)	802 (552)	885(640)
Reduction at Week 16 (dynes *sec/cm5) Mean (SD)	-162 (240)	-371 (429)	-181 (238)	-385 (396)
Geometric mean (Week 16/Baseline)	0.77	0.55	0.78	0.56
Treatment effect ratios (95% CL)		-29% (-39%, -18%)		-28% (-36%, -20%)
2-sided p-value		<0.0001		<0.0001

A consistent effect of OPSYNVI on reducing PVR was seen across subgroups of age, sex, race, geographical region, and baseline WHO FC (see Figure 2). Additionally, a consistent effect was observed in patients who were either treatment-naïve, or previously exposed to an ERA or PDE5 inhibitor.

Figure 2: Subgroup Analysis of the A DUE Study



The individual components of OPSYNVI, macitentan and tadalafil, have been approved and used independently or concomitantly in the clinical setting to effectively manage PAH. Macitentan is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to reduce the risks of disease progression and hospitalization for PAH. Tadalafil is a phosphodiesterase 5 (PDE5)

inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group 1) to improve exercise ability.

Macitentan

The primary efficacy endpoint of the multi-center, long-term, placebo-controlled SERAPHIN study was time to the first occurrence of death, a significant morbidity event, defined as atrial septostomy, lung transplantation, initiation of intravenous or subcutaneous prostanoids, or "other worsening of PAH" during double-blind treatment plus 7 days. Other worsening was defined as all of the following: 1) a sustained ≥15% decrease from baseline in 6-minute walk distance (6MWD), 2) worsening of PAH symptoms (worsening of WHO FC), and 3) need for additional treatment for PAH. All of these other worsening events were confirmed by an independent adjudication committee, blinded to treatment allocation.

Treatment with OPSUMIT 10 mg reduced the risk of clinical worsening events and hospitalization for PAH.

Tadalafil

The primary efficacy endpoint of a randomized, 16-week placebo-controlled study was the change from baseline at week 16 in 6-minute walk distance. Treatment with tadalafil 40 mg improved exercise ability.

16 HOW SUPPLIED/STORAGE AND HANDLING

OPSYNVI ® (macitentan and tadalafil) tablets, 10 mg/20 mg, are supplied as pink, oblong film-coated tablets debossed with "1020" on one side and "MT" on the other side.

OPSYNVI 10 mg/20 mg is supplied as follows:

7-count bottles with child-resistant closure NDC 66215-812-07
7-count blister NDC 66215-812-08
30-count bottle with child-resistant closure NDC 66215-812-30

OPSYNVI ® (macitentan and tadalafil) tablets, 10 mg/40 mg, are supplied as white to almost-white, oblong film-coated tablets debossed with "1040" on one side and "MT" on the other side.

OPSYNVI 10 mg/40 mg is supplied as follows:

10-count blister NDC 66215-814-10
30-count bottle with child-resistant closure NDC 66215-814-30

Store at 20ºC to 25ºC (68ºF to 77ºF); excursions are permitted between 15°C and 30°C (59°F and 86°F) *[see USP Controlled Room Temperature]*. Store and dispense in the original package to protect from moisture. Do not discard the desiccant.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Embryo-Fetal Toxicity

Counsel female patients of reproductive potential about the need to use reliable methods

of contraception during treatment with OPSYNVI and for one month after treatment discontinuation. Females of reproductive potential must have monthly pregnancy tests and must use reliable methods of contraception while taking OPSYNVI and for one month after discontinuing OPSYNVI *[see Use in Specific Populations (8.1)]* .

Macitentan-Containing Products REMS

For female patients, OPSYNVI is available only through a restricted program called the Macitentan-Containing Products REMS *[see Warnings and Precautions (5.2)]* . Male patients are not enrolled in the Macitentan-Containing Products REMS.

Patients may 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).

Advise patients to contact their gynecologist or healthcare provider if they want to change the form of birth control which is used to ensure that another acceptable form of birth control is selected.

Patients should be instructed to contact their physician if they suspect they may be pregnant. Patients should seek additional contraceptive advice from a gynecologist or similar expert as needed.

Inform female patients (and their guardians, if applicable) of the following notable requirements.

- Female patients must sign an enrollment form.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.3)]* .

Educate and counsel females of reproductive potential on the use of emergency contraception in the event of unprotected sex or contraceptive failure.

Advise pre-pubertal females to report any changes in their reproductive status immediately to her prescriber.

Review the Medication Guide and REMS educational materials with female patients.

Lactation

Advise women not to breastfeed during treatment with OPSYNVI *[see Use in Specific Populations (8.2)]* .

Infertility

Advise males of reproductive potential that OPSYNVI may impair fertility *[see Warnings and Precautions (5.11), Clinical Pharmacology (12.2), Use in Specific Populations (8.3), and Nonclinical Toxicology (13.1)].*

Hepatotoxicity

Some members of this pharmacological class are hepatotoxic. Educate patients on signs of hepatotoxicity. Advise patients that they should contact their doctor if they have unexplained nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching.

Hemoglobin Decrease

Advise patients that they may develop anemia. Advise patients that they will have blood

tests to check their red blood cells before starting OPSYNVI.

Use with Organic Nitrates or Guanylate Cyclase (GC) Stimulators

Inform patients of contraindication of OPSYNVI with any use of organic nitrates or GC stimulators.

Vision Loss

Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking OPSYNVI. Such an event may be a sign of NAION. Also discuss with patients that there is an increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE5 inhibitors.

Hearing Loss

Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking OPSYNVI. These events may be accompanied by tinnitus and dizziness.

Fluid Retention

Educate patients on signs of fluid retention. Advise patients that they should contact their doctor if they have unusual weight increase or swelling of the ankles or legs.

Administration

Patients should be advised not to cut, crush, or chew tablets.

Manufactured for:

Actelion Pharmaceuticals US, Inc.
a Janssen Pharmaceutical Company
Titusville, NJ 08560, USA

For patent information: www.janssenpatents.com

MEDICATION GUIDE
OPSYNVI ® (op-SIN-vee)
(macitentan and tadalafil)
tablets

Read this Medication Guide for OPSYNVI before you start taking OPSYNVI and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about OPSYNVI?

- **Serious birth defects.**

OPSYNVI can cause serious birth defects if taken during pregnancy.

- **Females must not be pregnant when they start taking OPSYNVI or become pregnant during treatment with OPSYNVI or for 1 month after stopping treatment with OPSYNVI.**
- Females who are able to get pregnant must have a negative pregnancy test before beginning treatment with OPSYNVI, each month during treatment with OPSYNVI and

1 month after stopping OPSYNVI.

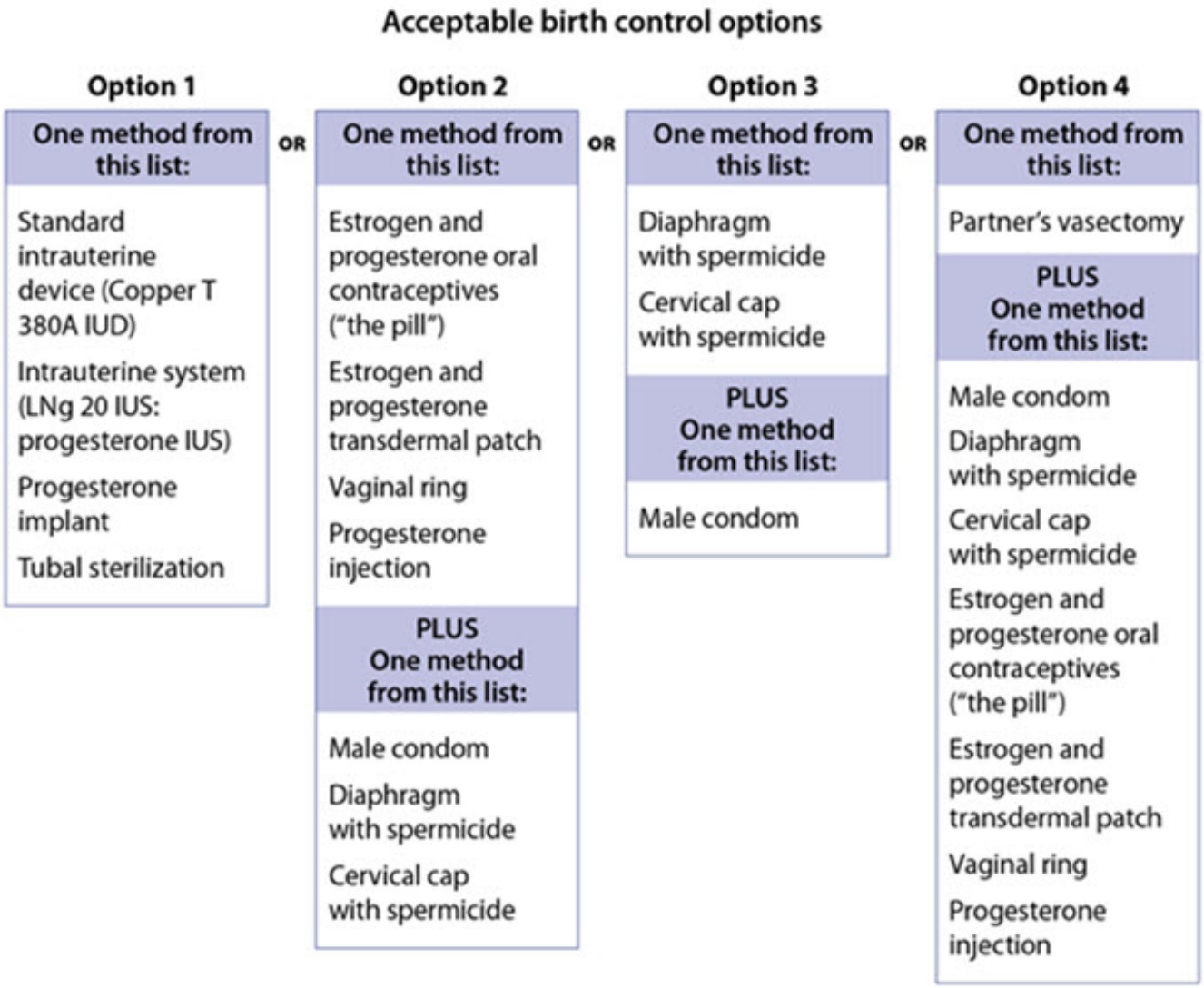
Talk to your healthcare provider about your menstrual cycle. Your healthcare provider will decide when to do the pregnancy test and will order a pregnancy test for you depending on your menstrual cycle.

- Females who <u>are able</u> to get pregnant are females who:
  - have entered puberty, even if they have not started their menstrual period, **and**
  - have a uterus, **and**
  - have not gone through menopause. Menopause means that you have not had a menstrual period for at least 12 months for natural reasons, or that you have had your ovaries removed.
- Females who <u>are not able</u> to get pregnant are females who:
  - have not yet entered puberty, **or**
  - do not have a uterus, **or**
  - have gone through menopause. Menopause means that you have not had a menstrual period for at least 12 months for natural reasons, or that you have had your ovaries removed, **or**
  - are infertile for other medical reasons and this infertility is permanent and cannot be reversed.

Females who are able to get pregnant must use 2 acceptable forms of birth control during treatment with OPSYNVI, and for 1 month after stopping OPSYNVI because the medicine may still be in the body.

- If you have had a tubal sterilization, have a progesterone implant, or have an IUD (intrauterine device), these methods can be used without another form of birth control.
- Talk with your healthcare provider or gynecologist (a doctor who specializes in female reproduction) to find out about options for acceptable birth control that you may use to prevent pregnancy during treatment with OPSYNVI.
- If you decide that you want to change the form of birth control that you use, talk with your healthcare provider or gynecologist to be sure that you choose another acceptable form of birth control.

See the chart below for Acceptable Birth Control Options during treatment with OPSYNVI.



- **Do not have unprotected sex.** Talk to your healthcare provider or pharmacist right away if you have unprotected sex or if you think your birth control has failed. Your healthcare provider may talk with you about using emergency birth control.
- **Tell your healthcare provider right away if you miss a menstrual period or think you may be pregnant.**

Females can only receive OPSYNVI through a restricted program called the Macitentan-Containing Products Risk Evaluation and Mitigation Strategy (REMS). If you are a female who can get pregnant, you must talk to your healthcare provider, understand the benefits and risks of OPSYNVI, and agree to all of the instructions in the Macitentan-Containing Products REMS.
Males can receive OPSYNVI without taking part in the Macitentan-Containing Products REMS.
See "**What are the possible side effects of OPSYNVI?**" for more information about side effects.

What is OPSYNVI?

- OPSYNVI is a prescription medicine that contains 2 medicines called macitentan and tadalafil. OPSYNVI is used for long-term treatment of adults with pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of your lungs.
- It is not known if OPSYNVI is safe and effective in children.

Who should not take OPSYNVI?

Do not take OPSYNVI if you:

- are pregnant, plan to become pregnant, or become pregnant during treatment with OPSYNVI. OPSYNVI can cause serious birth defects (see " What is the most important information I should know about OPSYNVI?")
- are allergic to macitentan, tadalafil, or any of the ingredients in OPSYNVI. See the end of this Medication Guide for a complete list of ingredients in OPSYNVI.
- take any medicines called nitrates
- take any medicines called guanylate cyclase (GC) stimulators

Before taking OPSYNVI, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems
- have low blood pressure
- have anemia
- have heart problems including heart attack or heart failure
- have pulmonary veno-occlusive disease (PVOD)
- have any eye problems, including NAION or an inherited eye disorder called retinitis pigmentosa
- have hearing problems such as ringing in the ears, dizziness, or loss of hearing
- have a deformed penis shape or Peyronie's disease or have blood cell problems such as sickle cell anemia, multiple myeloma, or leukemia. These conditions increase your risk of getting a prolonged erection.
- have kidney problems or get dialysis
- are pregnant or plan to become pregnant during OPSYNVI treatment. OPSYNVI can cause serious birth defects. See " **What is the most important information I should know about OPSYNVI?**"
- are breastfeeding or plan to breast feed. It is not known if OPSYNVI passes into your breastmilk. **Do not** breastfeed during treatment with OPSYNVI.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking OPSYNVI with other medicines may affect the way OPSYNVI and the other medicines work, and may increase your risk of side effects. **Do not** start any new medicine until you check with your healthcare provider.
Especially tell your healthcare provider if you take:

- nitrate medicines
- HIV medicines
- antifungal medicines
- antiseizure medicines
- medicines used to treat infection
- erectile dysfunction medicines
- blood pressure medicines
- medicines used to treat PAH or heart problems

Ask your healthcare provider or pharmacist if you are not sure if your medicine is one that is listed above. Know the medicines you take. Keep a list and show it to your healthcare provider or pharmacist when you get a new medicine.

How should I take OPSYNVI?

OPSYNVI will be mailed to you by a specialty pharmacy. Your healthcare provider will give you complete details.

- Take OPSYNVI exactly as your healthcare provider tells you to take it. **Do not** stop taking OPSYNVI unless your healthcare provider tells you.

- Take OPSYNVI with or without food.
- **Do not** cut, crush, or chew OPSYNVI tablets.
- If you take too much OPSYNVI, call your healthcare provider or go to the nearest hospital emergency room right away.
- If you miss a dose of OPSYNVI, take it as soon as you remember that day. Take the next dose at your regular time. **Do not** take 2 doses at the same time to make up for a missed dose.

What should I avoid while taking OPSYNVI?

- **Do not** have more than 4 alcohol-containing drinks in a short period of time during treatment with OPSYNVI. Drinking too much alcohol can increase your chances of getting low blood pressure, increased heart rate, dizziness, and headache.

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

- **Serious birth defects.** See " What is the most important information I should know about OPSYNVI?"
- **Liver problems**. OPSYNVI can cause liver problems. Your healthcare provider should do blood tests to check your liver before you start taking OPSYNVI. Tell your healthcare provider if you have any of the following symptoms of liver problems during treatment with OPSYNVI.
    - nausea or vomiting
    - pain in the upper right stomach
    - tiredness
    - loss of appetite
    - yellowing of your skin or whites of your eyes
    - dark urine
    - fever
    - itching
- **Decreased blood pressure (hypotension).** OPSYNVI can cause low blood pressure that lasts for a short time.
- **Low red blood cell levels (anemia) can occur with OPSYNVI treatment, usually during the first weeks after starting therapy.** Your healthcare provider will do blood tests to check your red blood cells before starting and as needed during treatment with OPSYNVI.
- **Vision loss.** OPSYNVI can cause decreased eyesight or permanent loss of vision in 1 or both eyes, which could be a sign of NAION. There is an increased risk of NAION in people who have already had NAION in 1 eye. If you notice a sudden decrease or loss of vision in 1 or both eyes, contact your healthcare provider right away.
- **Hearing problems.** Sudden decrease or loss of hearing, sometimes with ringing in the ears and dizziness, can happen during treatment with OPSYNVI. If you notice a sudden decrease or loss of hearing, contact your healthcare provider right away.
- **Fluid retention.** Fluid retention can happen within weeks after starting OPSYNVI and could lead to hospitalization. Tell your healthcare provider right away if you have any unusual weight gain, trouble breathing, or swelling of your ankles or legs. Your healthcare provider will look for the cause of any fluid retention and may stop treatment with OPSYNVI.
- **Decreased sperm count.** OPSYNVI can cause decreased sperm counts in males and may affect the ability to father a child. Tell your healthcare provider if being able to have children is important to you.

- **Prolonged erection.** Erections that last more than 4 hours, with or without pain, can happen during treatment with OPSYNVI. Painful erections (priapism) can cause permanent damage to the penis if not treated right away. Tell your healthcare provider right away if you have an erection that lasts longer than 4 hours, with or without pain.

The most common side effects of OPSYNVI include:
- too much fluid in your body (fluid retention) and swelling caused by too much fluid (edema)
- anemia
- headache, including migraine headache

These are not all the possible side effects of OPSYNVI.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store OPSYNVI?
- Store OPSYNVI tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Store OPSYNVI in the package that it comes in to protect from moisture.
- OPSYNVI contains a desiccant to help keep the tablets dry. **Do not** discard or eat the desiccant.
- OPSYNVI bottles have a child-resistant cap.
- **Keep OPSYNVI and all medicines out of the reach of children.**

General information about the safe and effective use of OPSYNVI.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use OPSYNVI for a condition for which it was not prescribed. Do not give OPSYNVI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about OPSYNVI that is written for health professionals.

What are the ingredients in OPSYNVI?
Active ingredients: macitentan and tadalafil
Inactive ingredients: tablet core: hydroxypropyl cellulose, hydroxypropyl cellulose (low substituted), lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate 80, povidone, sodium starch glycolate, sodium lauryl sulfate. **10 mg/20 mg film-coating:** hydroxypropyl methylcellulose, iron oxide red, iron oxide yellow, lactose monohydrate, talc, titanium dioxide, triacetin. **10 mg/40 mg film-coating:** hydroxypropyl methylcellulose, lactose monohydrate, talc, titanium dioxide, triacetin.
Manufactured for:
Actelion Pharmaceuticals US, Inc.
a Janssen Pharmaceutical Company
Titusville, NJ 08560, USA
For patent information: www.janssenpatents.com
For more information, call 1-800-526-7736 (1-800-JANSSEN), or visit www.OPSYNVI.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: 03/2024

PRINCIPAL DISPLAY PANEL - 10 mg/20 mg Tablet Bottle Carton

NDC 66215-812-30
Rx only

Opsynvi ®
(macitentan and tadalafil)
tablets

10 mg / 20 mg

Attention: Dispense the enclosed
Medication Guide to each patient.

30 film-coated tablets

PRINCIPAL DISPLAY PANEL - 10 mg/40 mg Tablet Bottle Carton

NDC 66215-814-30
Rx only

Opsynvi ®
(macitentan and tadalafil)
tablets

10 mg / 40 mg

Attention: Dispense the enclosed

Medication Guide to each patient.

30 film-coated tablets

OPSYNVI

macitentan and tadalafil tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:66215-814

Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MACITENTAN (UNII: Z9K9Y9WMVL) (MACITENTAN - UNII:Z9K9Y9WMVL)	MACITENTAN	10 mg
TADALAFIL (UNII: 742SXX0ICT) (TADALAFIL - UNII:742SXX0ICT)	TADALAFIL	40 mg

Inactive Ingredients

Ingredient Name	Strength
HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 9XZ8H6N6OH)	
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 2165RE0K14)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
POVIDONE K30 (UNII: U725QWY32X)	
SODIUM STARCH GLYCOLATE TYPE A (UNII: H8AV0SQX4D)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TRIACETIN (UNII: XHX3C3X673)	

Product Characteristics

Color	white (white to almost white)	**Score**	no score
Shape	OVAL (oblong)	**Size**	15mm
Flavor		**Imprint Code**	1040;MT
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:66215-814-30	1 in 1 CARTON	03/22/2024	
1		30 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:66215-814-10	1 in 1 CARTON	03/22/2024	
2	NDC:66215-814-01	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date

NDA	NDA218490	03/22/2024	

OPSYNVI

macitentan and tadalafil tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:66215-812
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MACITENTAN (UNII: Z9K9Y9WMVL) (MACITENTAN - UNII:Z9K9Y9WMVL)	MACITENTAN	10 mg
TADALAFIL (UNII: 742SXX0ICT) (TADALAFIL - UNII:742SXX0ICT)	TADALAFIL	20 mg

Inactive Ingredients

Ingredient Name	Strength
HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 9XZ8H6N6OH)	
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 2165RE0K14)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
POVIDONE K30 (UNII: U725QWY32X)	
SODIUM STARCH GLYCOLATE TYPE A (UNII: H8AV0SQX4D)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TRIACETIN (UNII: XHX3C3X673)	

Product Characteristics

Color	pink	**Score**	no score
Shape	OVAL (oblong)	**Size**	13mm
Flavor		**Imprint Code**	1020;MT
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:66215-812-07	1 in 1 CARTON	03/22/2024	

1		7 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:66215-812-30	1 in 1 CARTON	03/22/2024	
2		30 in 1 BOTTLE; Type 0: Not a Combination Product		
3	NDC:66215-812-08	1 in 1 CARTON	03/22/2024	
3	NDC:66215-812-01	7 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA218490	03/22/2024	

Labeler - Actelion Pharmaceuticals US, Inc. (002641228)

Establishment

Name	Address	ID/FEI	Business Operations
SMS Pharmaceuticals Limited		650460954	analysis(66215-812, 66215-814) , api manufacture(66215-812, 66215-814) , label(66215-812, 66215-814) , pack(66215-812, 66215-814)

Establishment

Name	Address	ID/FEI	Business Operations
SMS Pharmaceuticals Limited		677605501	analysis(66215-812, 66215-814)

Establishment

Name	Address	ID/FEI	Business Operations
Vimta Labs Limited		675597260	analysis(66215-812, 66215-814)

Establishment

Name	Address	ID/FEI	Business Operations
Lonza AG		480007517	analysis(66215-812, 66215-814) , api manufacture(66215-812, 66215-814)

Establishment

Name	Address	ID/FEI	Business Operations
Jetpharma SA		481885861	api manufacture(66215-812, 66215-814) , particle size reduction(66215-812, 66215-814)

Establishment

Name	Address	ID/FEI	Business Operations
PENN PHARMACEUTICAL SERVICES LIMITED		226277259	analysis(66215-812, 66215-814) , manufacture(66215-812, 66215-814)

Establishment

Name	Address	ID/FEI	Business Operations
Janssen Cilag SpA		542797928	analysis(66215-812, 66215-814)

Establishment

Name	Address	ID/FEI	Business Operations
Almac Pharma Services Limited		233170864	analysis(66215-812, 66215-814) , label(66215-812, 66215-814) , pack(66215-812, 66215-814)

Establishment

Name	Address	ID/FEI	Business Operations
Johnson & Johnson Private Limited		677603030	analysis(66215-812, 66215-814)