PDL DRUG REVIEW

Proprietary Name: Opsynvi®
Common Name: macitentan & tadalafil
PDL Category: Pulmonary Anti-Hypertensives

Comparable Products	Preferred Drug List Status
Ambrisentan	Preferred with Conditions
Sildenafil	Preferred with Conditions
Tadalafil	Preferred with Conditions

Pharmacology/Usage: Opsynvi® is a single tablet combination containing two oral components used to treat pulmonary arterial hypertension (PAH), including macitentan (an endothelin receptor antagonist [ERA]) and tadalafil (a phosphodiesterase 5 [PDE5] inhibitor).

Endothelin (ET)-1 and its receptors (ETA and ETB) mediate a variety of deleterious effects, such as vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation. Macitentan is an ERA that inhibits the binding of ET-1 to both ETA and ETB receptors.

Tadalafil is an inhibitor of 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 main phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by tadalafil increases the concentration of cGMP resulting in relaxation of pulmonary vascular smooth muscle cells and vasodilation of the pulmonary vascular bed.

Indication: 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.

There is no pregnancy category for this medication; however, the risk summary indicates that based on data from animal studies, Opsynvi® is contraindicated during pregnancy. Verify the pregnancy status of females of reproductive potential prior to starting treatment, monthly during treatment, and one month after stopping treatment. Refer to the Box warning for additional information. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets containing macitentan/tadalafil: 10mg/20mg and 10mg/40mg.

Do not cut, crush, or chew tablets.

Recommended Dosage: Obtain a pregnancy test in females of reproductive potential prior to Opsynvi® treatment, monthly during treatment and one month after stopping Opsynvi®. Start treatment in females of reproductive potential only after a negative pregnancy test.

Take PO QD with or without food. Swallow tablets whole, with water. If the patient misses a dose, take it as soon as possible and then take the next dose at the regularly scheduled time. Do not 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 is one 10mg/20mg tablet PO QD for one week. If tolerated, up titrate to one 10mg/40mg PO QD as the maintenance dose.

For patients transitioning from PDE5 inhibitor monotherapy or PDE5 inhibitor and ERA therapy in combination, the recommended dose is one 10mg/40mg PO QD.

The use of Opsynvi® is not recommended in patients undergoing dialysis. Avoid use in patients with severe renal impairment. For mild to moderate renal impairment, the dose should be consistent with the adult dosing. Opsynvi® was not studied in severe hepatic impairment and thus must not be initiated in patients with severe hepatic impairment, or clinically significant elevated hepatic aminotransferases. For patients with mild to moderate hepatic impairment, the recommended dose should be consistent with the adult dosing.

Drug Interactions: Administration of nitrates within 48 hours after the last dose of Opsynvi® is contraindicated.

Strong inducers of CYP3A4 such as rifampin, significantly reduce macitentan exposure. Use of Opsynvi® with strong CYP3A4 inducers should be avoided.

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.

Concomitant use of moderate dual inhibitors of CYP3A4 and CYP2C9, such as fluconazole, is predicted to increase macitentan exposure about 4-fold. Avoid concomitant use of Opsynvi® with moderate dual inhibitors of CYP3A4 and CYP2C9.

Concomitant treatment of both a moderate CYP3A4 inhibitor and moderate CYP2C9 inhibitor with Opsynvi® should be avoided.

PDE-5 inhibitors, including tadalafil, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure lowering-effects. In patients taking alpha-1 blockers, concomitant administration of tadalafil may lead to symptomatic hypotension in some patients. Thus, the combination of Opsynvi® and doxazosin is not recommended.

PDE-5 inhibitors, including tadalafil, are mild systemic vasodilators. Clinical 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.

Both alcohol and tadalafil 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 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.

Box Warning: Opsynvi® has a box warning regarding embryo-fetal toxicity. Do not administer Opsynvi® to a pregnant female because it may cause fetal harm. For females of reproductive potential, exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. In addition, 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).

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Opsynvi®) minus reported % incidence for macitentan. Please note that an incidence of 0% means the incidence was the same as or less than active comparator.* The most frequently reported adverse events included edema/fluid retention (7%), anemia (16%), headache (1%), abdominal pain (4%), hypotension (7%), myalgia (6%), nasopharyngitis (3%), nausea (6%), increased uterine bleeding (5%), back pain (2%), flushing (0%), vomiting (4%), palpitations (1%), pain in extremity (3%), and epistaxis (3%).

Listed % incidence for adverse drug reactions= reported % incidence for drug (Opsynvi®) minus reported % incidence for tadalafil. Please note that an incidence of 0% means the incidence was the same as or less than active comparator. The most frequently reported adverse events included edema/fluid retention

(5%), anemia (17%), headache (4%), abdominal pain (0%), hypotension (7%), myalgia (1%), nasopharyngitis (6%), nausea (0%), increased uterine bleeding (5%), back pain (0%), flushing (4%), vomiting (0%), palpitations (0%), pain in extremity (0%), and epistaxis (3%).

As mentioned in the box warning section, Opsynvi® is available for females only through a restricted program called the Macitentan-Containing Products REMS, because of the risk of embryo-fetal toxicity. Notable requirements of the Macitentan-Containing Products REMS include the following:

- Prescribers must be certified with the REMS by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the REMS prior to starting Opsynvi®. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraceptive requirements.
- Pharmacies must be certified with the REMS and must only dispense to patients who are authorized to receive Opsynvi®.
- Further information is available at www.MacitentanREMS.com or by calling 1-888-572-2934.

ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. Obtain liver enzyme tests prior to initiation of Opsynvi® and repeat during treatment as clinically indicated. Do not start Opsynvi® if elevated aminotransferases (> 3X upper limit of normal) at baseline.

Opsynvi® has vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing, 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 especially sensitive to actions of vasodilators.

Decreases in hemoglobin and hematocrit have occurred following ERA use and were observed in clinical studies with Opsynvi®. Decreases in hemoglobin rarely require transfusion. Initiation of Opsynvi® is not recommended in patients with severe anemia. Measure hemoglobin prior to the start of treatment and repeat during treatment as clinically indicated.

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Should signs of pulmonary edema occur when Opsynvi® tablets are administered, the possibility of associated PVOD should be considered. If confirmed, discontinue Opsynvi®.

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision, has been reported post marketing in temporal association with the use of PDE5 inhibitors. 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.

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.

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®. Monitor for signs of fluid retention after Opsynvi® initiation. If clinically significant fluid retention develops, assess the patient to determine the cause, and the possible need to discontinue Opsynvi®.

Tadalafil is also indicated for erectile dysfunction. The safety and efficacy of taking tadalafil tablets together with another PDE5 inhibitor or other treatments for erectile dysfunction have not been studied. Do not take other PDE5 inhibitors if taking Opsynvi®.

Macitentan, like other ERAs, may have an adverse effect on spermatogenesis. Counsel men about potential effects on fertility. In addition, there have been reports of prolonged erections greater than 4 hours and priapism for PDE5 inhibitors like tadalafil.

Contraindications:

- In females who are pregnant.
- In patients with a history of a hypersensitivity reaction to macitentan, tadalafil, or any component of the product.
- 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®.
- With the coadministration of guanylate cyclase (GC) stimulators, such as riociguat.

Manufacturer: Actelion Pharmaceuticals US, Inc., a Janssen Pharmaceutical Company

Analysis: The safety and efficacy of Opsynvi® were assessed in a multinational, multicenter, double-blind, adaptive, randomized, active-controlled, parallel-group study that included patients (N=187) with PAH (WHO FC II-III). The study was designed to compare the safety and efficacy of Opsynvi® to each monotherapy macitentan or tadalafil. Patients with pulmonary vascular resistance (PVR) of at least 240dyn.s/cm^5 were randomized to receive Opsynvi® (N=108), macitentan 10mg monotherapy (N=35), or tadalafil 40mg monotherapy (N=44), all 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 of included patients was 50 years (range 18-80), while 20% were ≥65 years of age. In addition, 22% were male, 62% were white, and at the time of enrollment, 51% were WHO FC II and 49% were WHO FC III.

The primary endpoint was the 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. Results suggested that Opsynvi® demonstrated greater reduction in PVR after 16 weeks. Treatment with Opsynvi® resulted in a statistically significant treatment effect of 0.71 (p<0.0001), representing a 29% reduction in PVR as compared to macitentan, and of 0.72 (p<0.0001) representing a 28% reduction in PVR as compared to tadalafil. Results of change from baseline in PVR at week 16 are presented in the table below, which was adapted from the prescribing information.

Change from baseline in PVR at week 16	Treatment-naïve & prior ERA treatment		Treatment-naïve & prior PDE5 inhibitor treatment	
	Macitentan (N=35)	Opsynvi® (N=70)	Tadalafil (N=44)	Opsynvi® (N=86)
Baseline, mean	816	834	802	885
Reduction at week 16, mean	-162	-371	-181	-385
Geometric mean (week 16/baseline)	0.77	0.55	0.78	0.56
Treatment effect ratios		-29%		-28%
2-sided p-value		<0.0001		<0.0001

The individual components of Opsynvi® have been approved and used independently or concomitantly in the clinical setting to effectively manage PAH. Macitentan is an ERA indicated for the treatment of PAH (WHO Group I) to reduce the risks of disease progression and hospitalization for PAH. Tadalafil is a PDE5 inhibitor indicated for the treatment of PAH (WHO Group I) to improve exercise ability.

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

prostanoid, or “other worsening of PAH’ during double-blind treatment plus 7 days. Treatment with Opsumit® 10mg (macitentan) reduced the risk of clinical worsening events and hospitalization for PAH.

Place in Therapy: Opsynvi® is a single-tablet combination containing 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. It has a box warning regarding embryo-fetal toxicity and is available for all female patients only through a restricted program called the Macitentan-Containing Products Risk Evaluation and Mitigation Strategy (REMS). The safety and efficacy of Opsynvi® were assessed in a multicenter, double-blind, active-controlled study that included patients (N=187) with PAH (WHO FC II-III). Results suggested that Opsynvi® demonstrated greater reduction in PVR after 16 weeks. Treatment with Opsynvi® resulted in a statistically significant treatment effect of 0.71 ($p<0.0001$) representing a 29% reduction in PVR as compared to macitentan and of 0.72 ($p<0.0001$) representing a 28% reduction in PVR as compared to tadalafil. Opsynvi® is the first FDA approved once-daily single-tablet combination treatment for PAH.

Summary

There is some evidence at this time from a phase 3 study to suggest that Opsynvi® may be more effective than each of its individual ingredients as monotherapy (macitentan and tadalafil) for the primary endpoint of change from baseline in PVR; however, there is no evidence at this time to support that Opsynvi® is safer or more effective than the other currently preferred, more cost-effective medications, including using the combination of macitentan and tadalafil. It is therefore recommended that Opsynvi® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement:
- ☐ **Preferred**
- ☒ **Non-Preferred with Conditions**

References

[1] Opsynvi® [package insert]. Titusville, NJ: Actelion Pharmaceuticals US, Inc., a Janssen Pharmaceutical Co; 2024.