BlueCross BlueShield
Federal Employee Program
Blue Cross Blue Shield Association
750 9th St NW, Suite 900
Washington, D.C. 20001
1-800-624-5060
Fax 1-877-378-4727

5.40.037

Section:	Prescription Drugs	**Effective Date:**	October 1, 2025
Subsection:	Cardiovascular Agents	**Original Policy Date:**	May 17, 2024
Subject:	Opsynvi	**Page:**	1 of 8

Last Review Date: September 19, 2025

Opsynvi

Description

Opsynvi (macitentan and tadalafil)

Background

Pulmonary arterial hypertension is a rare disorder of the pulmonary arteries in which the pulmonary arterial pressure rises above normal levels in the absence of left ventricular failure. This condition can progress to cause right-sided heart failure. Opsynvi is indicated for treatment of pulmonary arterial hypertension (PAH) which is classified by WHO as Group 1. Opsynvi is used to treat pulmonary arterial hypertension (PAH, high blood pressure in the lungs) to improve exercise ability (1).

The World Health Organization (WHO) has classified pulmonary hypertension into five different groups: (2)

WHO Group 1: Pulmonary Arterial Hypertension (PAH)

1.1 Idiopathic (IPAH)
1.2 Heritable PAH
  1.2.1 Germline mutations in the bone morphogenetic protein receptor type 2 (BMPR2)
  1.2.2 Activin receptor-like kinase type 1 (ALK1), endoglin (with or without hereditary hemorrhagic telangiectasia), Smad 9, caveolin-1 (CAV1), potassium channel super family K member-3 (KCNK3)
  1.2.3 Unknown
1.3 Drug-and toxin-induced
1.4 Associated with:
  1.4.1 Connective tissue diseases

1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis

1'. Pulmonary vena-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

1''. Persistent pulmonary hypertension of the newborn (PPHN)

The diagnosis of WHO Group 1 PAH requires a right heart catheterization to demonstrate an mPAP ≥ 20mmHg at rest and a pulmonary vascular resistance (PVR) ≥ 3 Wood units, mean pulmonary capillary wedge pressure ≤ 15mmHg (to exclude pulmonary hypertension due to left heart disease, i.e., WHO Group 2 pulmonary hypertension) (4-6).

WHO Group 2: Pulmonary Hypertension Owing to Left Heart Disease

2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

WHO Group 3: Pulmonary Hypertension Owing to Lung Disease and/or Hypoxia

3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental abnormalities

WHO Group 4: Chronic Thromboembolic Pulmonary Hypertension <CTEPHl

WHO Group 5: Pulmonary Hypertension with Unclear Multifactorial Mechanisms

5.1 Hematologic disorders: Chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3 Metabolic disorders: glycogen storage disease, Gaucher's disease, thyroid disorders

5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis, segmental PH

The American College of Chest Physicians (ACCP) has published an updated clinical practice guidelines for treating PAH. These guidelines use the New York Heart Association (NYHA) functional classification of physical activity scale to classify PAH patients in classes I-IV based on the severity of their symptoms (3). Opsynvi is indicated for patients with NYHA Functional Class II and III (1).

Class I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.
Class II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. These patients are comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. These patients are comfortable at rest, but less than ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.
Class IV	Patients with pulmonary hypertension resulting in inability to perform any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present at rest, and discomfort is increased by any physical activity.

(3)

Regulatory status

FDA-approved indication: Opsynvi is a combination of macitentan, an endothelin receptor antagonist (ERA), and tadalafil, phosphodiesterase 5 (PDE5) inhibitor, indicated for the chronic treatment of pulmonary arterial hypertension (PAH, WHO Group I) in adult patients of WHO functional class (FC) II-III. Individually, macitentan reduces risk of clinical worsening events and hospitalization, and tadalafil improves exercise ability (1).

Opsynvi contains a boxed warning for embryo-fetal toxicity. Females of childbearing potential should have pregnancy excluded before the start of treatment with Opsynvi. Advise use of effective contraception before initiation, during treatment, and for one month after treatment with Opsynvi(1).

Hepatotoxicity has occurred with Opsynvi use. Patients should have a baseline liver function test and be monitored during treatment as clinically indicated. Additionally, there have been post-administration reports of decreases in hemoglobin concentration and hematocrit that have

resulted in anemia. It is recommended that hemoglobin concentrations be checked prior to treatment and repeated during treatment as clinically indicated. Should signs of pulmonary edema occur, consider the possibility of associated pulmonary veno-occlusive disease and consider whether Opsynvi should be discontinued (1).

Opsynvi is not recommended for use in patients with a creatinine clearance less than 30 mL/min, as patients with severe renal impairment have increased exposure to the tadalafil component of Opsynvi. Patients using dialysis also should not receive Opsynvi (1).

Visual loss has been reported postmarketing in temporal association with the use of tadalafil and other PDE5 inhibitors. Most patients had underlying anatomic or vascular risk factors for the development of non-arteritic anterior ischemic neuropathy (NAION), therefore use of Opsynvi is not recommended in patients with hereditary degenerative retinal disorders (1).

Sudden hearing loss has been reported in patients taking tadalafil. However, it has not been determined if these events are caused by tadalafil or PDE5 inhibitors or are due to other factors (1).

The use of Opsyvni is contraindicated in patients who are using any form of organic nitrate, either regularly or intermittently. Opsynvi potentiates the hypotensive effect of nitrates. This potentiation is thought to result from the combined effects of nitrates and the tadalafil component of Opsynvi on the nitric oxide/cGMP pathway. Opsynvi is also contraindicated in patients on guanylate cyclase (GC) stimulators (1).

The safety and efficacy of Opsynvi in children have not been established (1).

Related policies
Adcirca, Adempas, Flolan/Veletri, Letairis, Opsumit, Orenitram, PDE5 Inhibitor powders, Remodulin, Revatio, Tracleer, Tyvaso, Uptravi, Ventavis, Winrevair

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Opsynvi may be considered **medically necessary** if the conditions indicated below are met.

Opsynvi may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 18 years of age or older

Diagnosis

Patient must have the following:

1. Pulmonary Arterial Hypertension (PAH) - **WHO Group I**
    a. NYHA functional **class II or III**

AND NONE of the following:

1. Concurrent therapy with any nitrates (in any form)
2. Concurrent therapy with another phosphodiesterase 5 (PDE5) inhibitor
3. Concurrent therapy with guanylate cyclase (GC) stimulators
4. Concurrent therapy with alpha blockers
5. Severe hepatic impairment (Child-Pugh Class C)
6. Severe renal impairment (creatinine clearance <30 mL/min)

AND ALL of the following:

1. Absence of clinically significant anemia
2. Prescribed by or recommended by a cardiologist or pulmonologist
3. Prescriber agrees to monitor for pulmonary edema and discontinue if confirmed
4. Prescriber agrees to counsel and evaluate the patient for sudden loss of vision or hearing associated with this medication
5. Females of reproductive potential **only**: patient should have pregnancy excluded before the start of treatment with Opsynvi and patient should be advised to use effective contraception during treatment and for one month after the last dose

Prior – Approval *Renewal* Requirements

Age 18 years of age or older

Diagnosis

Patient must have the following:

1. Pulmonary Arterial Hypertension (PAH) - **WHO Group I**

AND NONE of the following:

a. Concurrent therapy with any nitrates (in any form)
b. Concurrent therapy with another phosphodiesterase 5 (PDE5) inhibitor
c. Concurrent therapy with guanylate cyclase (GC) stimulators
d. Concurrent therapy with alpha blockers
e. Severe hepatic impairment (Child-Pugh Class C)
f. Severe renal impairment (creatinine clearance <30mL/min)

AND ALL of the following:

1. Symptoms have improved or stabilized
2. Prescriber agrees to monitor for pulmonary edema and discontinue if confirmed
3. Prescriber agrees to counsel and evaluate the patient for sudden loss of vision or hearing associated with this medication
4. Females of reproductive potential **only**: patient should be advised to use effective contraception during treatment with Opsynvi and for one month after the last dose

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity 90 tablets per 90 days

Duration 2 years

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary
Pulmonary arterial hypertension is a rare disorder of the pulmonary arteries in which the pulmonary arterial pressure rises above normal levels in the absence of left ventricular failure. This condition can progress to cause right-sided heart failure. Opsynvi is a combination of an endothelin receptor antagonist and a phosphodiesterase 5 inhibitor, indicated for treatment of pulmonary arterial hypertension (WHO Group I in patients with NYHA class II or III to improve exercise ability and to decrease clinical worsening (1).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Opsynvi while maintaining optimal therapeutic outcomes.

References

1. Opsynvi [package insert]. Titusville, NJ: Actelion Pharmaceuticals US, Inc; April 2025.
2. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll* Cardiol. 2013; 62:034-841.
3. Taichman DB, Ornelas J, Chung L, et al. Pharmacologic therapy for pulmonary arterial hypertension in adults. CHEST guideline and expert panel report. *Chest.* 2014. 46(2):449-475.
4. Simonneau G, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1) Epub 2019 Jan 24.
5. Rose-Jones LJ and Mclaughlin V. Pulmonary Hypertension: Types and Treatments. Curr Cardiol Rev. 2015 Feb; 11(1): 73–79.
6. Rudolf KF, et al. Usefulness of pulmonary capillary wedge pressure as a correlate of left ventricular filling pressures in pulmonary arterial hypertension. The Journal of Heart and Lung Transplantation, Vol33, No2. February 2014.

Policy History

Date	Action
May 2024	Addition to PA
September 2024	Annual review
March 2025	Annual review
June 2025	Per PI update, removed REMS requirement
September 2025	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 19, 2025 and is effective on October 1, 2025.