BlueCross BlueShield
Federal Employee Program

OPSYNVI
(macitentan and tadalafil)

RATIONALE FOR INCLUSION IN PA PROGRAM

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

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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 <CTEPHI

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).

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

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5. Rose-Jones LJ and Mclaughlin V. Pulmonary Hypertension: Types and Treatments. Curr Cardiol Rev. 2015 Feb; 11(1): 73–79.
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