



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. Opsumit is indicated for treatment of pulmonary arterial hypertension (PAH) which is classified by WHO as Group 1. Opsumit 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 \geq 20mmHg at rest and a pulmonary vascular resistance (PVR) \geq 3 Wood units, mean



pulmonary capillary wedge pressure \leq 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 <CTEPH

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). Opsumit 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.	(3)
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	

Regulatory status

FDA-approved indication: Opsumit 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. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment) (1).

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

Hepatotoxicity has occurred with Opsumit 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 Opsumit should be discontinued (1).

The recommended dosage of Opsumit is 10 mg once daily for oral administration. Doses higher than 10 mg once daily have not been studied in patients with PAH and are not recommended (1).

The safety and effectiveness of Opsumit in pediatric patients 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. Opsumit is an endothelin receptor antagonist 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 Opsumit while maintaining optimal therapeutic outcomes.

References

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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.
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