



RATIONALE FOR INCLUSION IN PA PROGRAM

Background

Tyvaso (treprostinil) is a prostacyclin analogue. Tyvaso's major pharmaceutical actions are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. Tyvaso is indicated for the treatment of pulmonary hypertension (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 (2). 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). Tyvaso is indicated for PAH patients with NYHA Functional Class III symptoms (1).



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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 indications: Tyvaso is a prostacyclin mimetic indicated for the treatment of: (1)

- Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies establishing effectiveness predominantly included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).
- Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%).

Tyvaso is a pulmonary and systemic vasodilator, concomitant administration of Tyvaso with diuretics, antihypertensive agents or other vasodilators may increase the risk of symptomatic hypotension. In patients with low systemic arterial pressure, Tyvaso may cause symptomatic hypotension (1).

Tyvaso inhibits platelet aggregation so there may be an increased risk of bleeding, particularly in



patients receiving anticoagulants (1).

Tyvaso may cause acute bronchospasm. Patients with asthma or chronic obstructive pulmonary disease (COPD), or other bronchial hyperreactivity, are at increased risk for bronchospasm. Patients should be optimally treated for reactive airway disease prior to and during treatment with Tyvaso (1).

Safety and effectiveness in pediatric patients less than 18 years of age have not been established (1).

Summary

Tyvaso (treprostinil) is a prostacyclin analogue. Tyvaso's major pharmaceutical actions are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. Tyvaso is indicated for the treatment of pulmonary hypertension. Safety and effectiveness of Tyvaso in patients less than 18 years of age have not been established (1).

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

References

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