



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 and death (1). Epoprostenol is indicated for treatment of pulmonary arterial hypertension (PAH) which is classified by WHO as Group 1. Epoprostenol is used to treat pulmonary arterial hypertension (PAH, high blood pressure in the lungs) to improve exercise ability (1-2).

The World Health Organization (WHO) has classified pulmonary hypertension into five different groups: (3)

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) (5-7).

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 guideline 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 (4). Epoprostenol is indicated for patients with NYHA Functional Class III or IV (1-2).

**FLOLAN / VELETRI
(epoprostenol)**

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.

(4)

Regulatory Status

FDA-approved indication: Epoprostenol is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity. Studies establishing effectiveness included predominantly (97%) patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH (49%) or PAH associated with connective tissue diseases (51%) (1-2).

Some patients with pulmonary hypertension have developed pulmonary edema during dose initiation, which may be associated with pulmonary veno-occlusive disease. Epoprostenol should not be used chronically in patients who develop pulmonary edema during dose initiation (1-2).

Epoprostenol is associated with a variety of adverse effects, many of which can be dose-limiting such as hypotension, nausea, vomiting, flushing, and headache. Hemorrhage, thrombocytopenia, and sepsis have also been reported (1-2).

Epoprostenol is contraindicated in patients with heart failure caused by reduced left ventricular ejection fraction (1-2).

Summary

**FLOLAN / VELETRI
(epoprostenol)**

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 and death. Epoprostenol is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) and NYHA functional class III or IV to improve exercise capacity (1-2).

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

References

1. Flolan [package insert]. Research Triangle Park, NC: GlaxoSmithKline; October 2023.
2. Veletri [package insert]. Titusville, NJ: Janssen Pharmaceutical Company; July 2022.
3. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013; 62:034-841.
4. 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.
5. Simonneau G, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53(1) Epub 2019 Jan 24.
6. Rose-Jones LJ and McLaughlin V. Pulmonary Hypertension: Types and Treatments. *Curr Cardiol Rev*. 2015 Feb; 11(1): 73–79.
7. 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.