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 (1-2). Uptravi is indicated for treatment of pulmonary arterial hypertension (PAH) which is classified by WHO as Group 1. Uptravi 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)

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. Uptravi is indicated for patients with NYHA Functional Class III symptoms (3).

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<th>Class</th>
<th>Description</th>
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<td>Class I</td>
<td>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.</td>
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<td>Class II</td>
<td>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.</td>
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</table>
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: Uptravi is a prostacyclin receptor agonist indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH. Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms (1).

Uptravi should be discontinued if signs or symptoms of pulmonary edema occur (1).

For patients who do not have a positive acute vasodilator testing and are considered lower risk based on clinical assessment, oral therapy with endothelin receptor antagonist (ERA) or phosphodiesterase type 5 inhibitor (PDE-5I) would be the first line of therapy recommended (4).

Safety and efficacy 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 and death. Uptravi is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in patients with NYHA class II-III symptoms (1).

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

References