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). Adempas is indicated for the treatment of two types of pulmonary arterial hypertension (PAH) which is high blood pressure in the lungs. Adempas is indicated for the treatment of patients with PAH (WHO Group 1) to improve exercise capacity, improve their functional class and to delay clinical worsening. It is also indicated for adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and functional class (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 ≥ 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 <CTEPHl

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 (3). 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). Adempas was studied in all four NYHA classes and the majority of efficacy was shown with /NYHA functional class II-IV (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 indications: Adempas is a soluble guanylate cyclase (sGC) stimulator indicated for the treatment of adults with: (1)

1. Persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class.
2. Pulmonary Arterial Hypertension (PAH) (WHO Group 1) to improve exercise capacity, improve WHO functional class and to delay clinical worsening.

Adempas has a boxed warning of embryo-fetal toxicity. Adempas must not be administered to pregnant females because it may cause fetal harm. Females with reproductive potential must have a negative pregnancy test prior to starting treatment, monthly during treatment and for one

month after treatment discontinuation. Pregnancy prevention using effective contraception must be done during treatment and for one month after treatment is discontinued. Regardless of reproductive potential, all female patients must enroll in the Adempas REMS Program and it is only available through a restricted distribution program (1).

Co-administration of Adempas with other soluble guanylate cyclase (sGC) stimulators, or nitrates, or nitric oxide donors, in any form, is contraindicated. Concomitant administration of Adempas with phosphodiesterase (PDE) inhibitors, including specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is also contraindicated (1).

The use of Adempas is not recommended for patients with a creatinine clearance <15 ml/min or on dialysis. It is also not recommended for patients with severe hepatic impairment (Child Pugh C) (1).

Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors. Consider a dose reduction if patient develops signs or symptoms of hypotension (1).

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and, if confirmed, discontinue treatment with Adempas (1).

Safety and efficacy in pediatric patients have not been established (1).

Summary

Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (WHO Group I) that are NYHA functional class II-IV or with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) (WHO Group 4) after surgical treatment or

inoperable CTEPH. Adempas is contraindicated with concurrent therapy with any nitrates or nitric oxide donors, sGC stimulators, and/or phosphodiesterase (PDE-5) inhibitors. Adempas is not recommended in patients with a creatinine clearance that is <15 ml/min, if the patient is on dialysis, and in severe hepatic impairment (Child Pugh C). Adempas has a boxed warning addressing fetal harm to pregnant females. Pregnancy must be excluded and avoided. A REMS program is necessary for female patients and their physicians to be enrolled in (1).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Adempas 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.
6. 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.