

**REVATIO, LIQREV (sildenafil)****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. Revatio/Liqrev is approved for treatment of pulmonary arterial hypertension (PAH) which is classified by WHO as Group 1 to improve exercise ability and delay clinical worsening. Sildenafil, at different dosages, is also marketed as Viagra for the treatment of erectile dysfunction which is a plan exclusion (1-3).

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 (e.g. pulmonary artresia)

1.4.5 Schistosomiasis

1'. Pulmonary vena-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

1". Persistent pulmonary hypertension of the newborn (PPHN)

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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) (8-10).

**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

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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. Revatio/Liqrev is indicated for patients with NYHA Functional Class II and III symptoms (1-2, 6).

**ADULT NYHA FUNCTIONAL CLASS CHART**

|           |   |
|-----------|---|
| 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)

**CHILDRENS NYHA FUNCTIONAL CLASS CHART**

|           |   |
|-----------|---|
| Class I   | Asymptomatic  |
| Class II  | Mild tachypnea or diaphoresis with feeding in infants<br>Dyspnea on exertion in older children  |
| Class III | Marked tachypnea or diaphoresis with feeding in infants<br>Marked dyspnea on exertion.<br>Prolonged feeding times with growth failure |

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| Class IV | Symptoms such as tachypnea, retractions, grunting, or diaphoresis at rest |
|----------|---|

These guidelines recommend that oral therapy with a phosphodiesterase inhibitor (sildenafil) be used as first-line therapy for NYHA Class II and III patients (4). Revatio/Liqrev (sildenafil) is the same therapeutic class as Adcirca (tadalafil) and has the same indication for PAH (WHO group 1).

**Regulatory Status**

FDA-approved indications: (1-2)

- Revatio/Liqrev is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening. Studies establishing effectiveness included predominately patients with NYHA Functional Class II-III symptoms. Etiologies were idiopathic (primary) pulmonary hypertension, or pulmonary hypertension associated with connective tissue disease.
- Revatio is indicated in pediatric patients 1 to 17 years old for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and, in pediatric patients too young to perform standard exercise testing, pulmonary hemodynamics thought to underly improvements in exercise.

**Off-Label Uses:**

- Revatio/Liqrev may be used off-label for the treatment of Raynaud's syndrome. In this syndrome patients experience temperature-sensitive digital vasospasm leading to cyanotic skin, usually in the digits. Sildenafil increases the capillary blood flow velocity in patients with therapy-resistant Raynaud's syndrome (7).
- Revatio/Liqrev may be used off-label for the treatment of pediatrics with PAH. PDE-5 expression and activity are increased in PAH and specific PDE-5 inhibitors such as sildenafil or tadalafil increase smooth muscle cell cGMP levels and promote pulmonary vascular dilation and remodeling in pediatric patients (6).

The use of Revatio/Liqrev is contraindicated in patients who are using any form of organic

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nitrate, either regularly or intermittently. Revatio/Liqrev potentiates the hypotensive effect of nitrates. This potentiation is thought to result from the combined effects of nitrates and sildenafil on the nitric oxide/cGMP pathway. Revatio/Liqrev is also contraindicated with riociguat (1-2).

The efficacy of Revatio/Liqrev has not been adequately evaluated in patients taking bosentan concurrently (1-2).

### **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. Revatio/Liqrev is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and delay clinical worsening. Revatio may also be used off-label for treatment therapy-resistant Raynaud's syndrome (1-2, 4).

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

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