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PDE5 INHIBITOR POWDERS
Sildenafil powder, Tadalafil powder

RATIONALE FOR INCLUSION IN PA PROGRAM

Background

Sildenafil and tadalafil are marketed as Revatio and Adcirca respectively for pulmonary arterial hypertension (PAH). This 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 and Adcirca received approval for treatment of pulmonary arterial hypertension (PAH) which is classified by WHO as Group 1. Revatio and Adcirca are used to treat pulmonary arterial hypertension (PAH, high blood pressure in the lungs) to improve the exercise ability. Tadalafil also comes as Cialis which is approved to treat the signs and symptoms of benign prostatic hyperplasia (BPH), a condition in which the prostate gland becomes enlarged (1-9).

Sildenafil and tadalafil, at different dosages, are also marketed as Viagra and Cialis respectively for the treatment of erectile dysfunction which is a **plan exclusion** (3-4).

The World Health Organization (WHO) has classified pulmonary hypertension into five different groups: (5)

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

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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 <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

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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 is indicated for patients with NYHA Functional Class II and III symptoms (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.

(5)

CHILDRENS NYHA FUNCTIONAL CLASS CHART

Class I	Asymptomatic.
Class II	Mild tachypnea or diaphoresis with feeding in infants Dyspnea on exertion in older children
Class III	Marked tachypnea or diaphoresis with feeding in infants Marked dyspnea on exertion Prolonged feeding times with growth failure
Class IV	Symptoms such as tachypnea, retractions, grunting, or diaphoresis at rest

(7

These guidelines recommend that oral therapy with a phosphodiesterase inhibitor (sildenafil) be used as first-line therapy for NYHA Class II and III patients (5). Adcirca (tadalafil) is the same therapeutic class as Revatio (sildenafil) and has the same indication for PAH (WHO group 1).

Regulatory Status

FDA-approved indications (1-3):

- Revatio and Adcirca are phosphodiesterase 5 (PDE5) inhibitors 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 (71%) or pulmonary hypertension associated with connective tissue disease (25%).

- 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.
- Cialis is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of erectile dysfunction (ED), the signs and symptoms of benign prostatic hyperplasia (BPH) and ED.

Off-Label Uses:

Revatio 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).

Adcirca and Revatio may be used off label for the treatment of pediatric with PAH. PDE5 expression and activity are increased in PAH and specific PDE5 inhibitors such as sildenafil or tadalafil increase smooth muscle cell cGMP levels and promote pulmonary vascular dilation and remodeling in pediatric patients (8).

The use of sildenafil and tadalafil are contraindicated in patients who are using any form of organic nitrate, either regularly or intermittently. Revatio potentiates the hypotensive effect of nitrates. This potentiation is thought to result from the combined effects of nitrates and Revatio on the nitric oxide/cGMP pathway. Revatio is also contraindicated with riociguat (1-4).

Tadalafil is not indicated for use in pediatric patients. Safety and efficacy in patients below the age of 18 years has not been established (3).

Summary

Sildenafil and tadalafil are marketed as Revatio and Adcirca for pulmonary arterial hypertension.

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

References

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