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Preferred products: Alyq, tadalafil

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. Tadalafil received approval for treatment of pulmonary arterial hypertension (PAH) which is classified by WHO as Group 1. Adcirca/Alyq/Tadliq is used to treat pulmonary arterial hypertension (PAH, high blood pressure in the lungs) to improve the exercise ability. Tadalafil, at different dosages, is currently also marketed as Cialis for the treatment of erectile dysfunction (1-3).

The World Health Organization (WHO) has classified pulmonary hypertension into five different groups: (4)

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 atresia)
- 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 ≥ 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) (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 <CTEPHI

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,

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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. 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 (5). Adcirca/Alyq/Tadliq is indicated for patients with NYHA Functional Class II and III symptoms (1-3).

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.

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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

(5)

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/Alyq (tadalafil) is the same therapeutic class as Revatio (sildenafil) and has the same indication for PAH (WHO group 1).

Regulatory Status

FDA-approved indication: Adcirca/Alyq/Tadliq is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II – III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%) (1-3).

Off-Label Uses:

Adcirca/Alyq/Tadliq 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 (7).

The use of Adcirca/Alyq/Tadliq is contraindicated in patients who are using any form of organic nitrate, either regularly or intermittently. Adcirca/Alyq/Tadliq potentiates the hypotensive effect of nitrates. This potentiation is thought to result from the combined effects of nitrates and Adcirca/Alyq/Tadliq on the nitric oxide/cGMP pathway. Adcirca/Alyq/Tadliq is also contraindicated in patients on guanylate cyclase (GC) stimulators (1-3).

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Adcirca/Alyq/Tadliq is not recommended for use in patients with a creatinine clearance less than 30 mL/min, as patients with severe renal impairment have increased exposure to tadalafil. Patients using dialysis also should not receive Adcirca/Alyq/Tadliq (1).

Visual loss has been reported postmarketing in temporal association with the use of tadalafil and other PDE5 inhibitors. Most patients had underlying anatomic or vascular risk factors for the development of non-arteritic anterior ischemic neuropathy (NAION), therefor use of Adcirca/Alyq/Tadliq is not recommended in patients with hereditary degenerative retinal disorders (1).

Sudden hearing loss has been reported in patients taking tadalafil. However, it has not been determined if these events are caused by Adcirca/Alyq/Tadliq l or PDE5 inhibitors or are due to other factors (1).

Appropriate studies have not been performed on the relationship of age to the effects of Adcirca/Alyq/Tadliq in the pediatric population. Safety and efficacy have not been established (1-3).

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. Adcirca/Alyq/Tadliq is used to treat pulmonary arterial hypertension (PAH, high blood pressure in the lungs) to improve exercise ability (1-3).

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

References

1. Adcirca [package insert]. Indianapolis, IN: Eli Lilly and Company; September 2020.
2. Alyq [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; April 2023.

3. Tadliq [package insert]. Farmville, NC: CMP Pharma, Inc.; October 2023.
4. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll* Cardiol. 2013; 62:034-841.
5. 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.
6. Ross RD, Bollinger RO, Pinsky WW. Grading the severity of congestive heart failure in infants. Pediatr Cardiol. 1992;13:72–5.
7. Abman SH; Hansmann G; Archer SL et al. Pediatric Pulmonary Hypertension: Guidelines from the American Heart Association and American Thoracic Society. Circulation. 2015; 132(21): 2037-99.
8. Simonneau G, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1) Epub 2019 Jan 24.
9. Rose-Jones LJ and Mclaughlin V. Pulmonary Hypertension: Types and Treatments. Curr Cardiol Rev. 2015 Feb; 11(1): 73–79.
10. 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.