BlueCross BlueShield
Federal Employee Program
Blue Cross Blue Shield Association
750 9th St NW, Suite 900
Washington, D.C. 20001
1-800-624-5060
Fax 1-877-378-4727

5.40.023

Section:	Prescription Drugs	**Effective Date:**	October 1, 2024
Subsection:	Cardiovascular Agent	**Original Policy Date:**	December 6, 2013
Subject:	PDE5 inhibitor powders	**Page:**	1 of 10

Last Review Date: September 6, 2024

PDE5 inhibitor powders

Description

Sildenafil powder, Tadalafil powder

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
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

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).

Related policies

Adcirca, Adempas, Cialis, Flolan/Veletri, Letairis, Opsumit, Opsynvi, Orenitram, Remodulin, Revatio, Tracleer, Tyvaso, Uptravi, Ventavis, Winrevair

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.
Sildenafil and **tadalafil powders** may be considered **medically necessary** if the conditions indicated below are met.

Sildenafil and **tadalafil powders** may be considered **investigational** for all other indications.

Prior-Approval Requirements

Diagnoses

Patient must have **ONE** of the following

Sildenafil and Tadalafil Powders

1. Pulmonary arterial hypertension (PAH) – WHO Group I
    a. NYHA functional classification of physical activity – Class II or III
    b. Prescribed by or recommended by a cardiologist or pulmonologist
    c. Prescriber agrees to counsel and evaluate the patient for sudden loss of vision or hearing associated with this medication
    d. **NO** concurrent therapy with **ALL** of the following:
        i. Any nitrates (in any form)
        ii. Another PDE-5 inhibitor
        iii. Guanylate cyclase (GC) stimulators
        iv. Alpha blockers
    e. **Tadalafil powder only**: **NO** severe hepatic impairment (Child-Pugh Class C) **AND NO** severe renal impairment (creatinine clearance <30 mL/min)
    f. The requested **oral** dose does not exceed 20mg / unit

Sildenafil Powder Only

1. Raynaud's syndrome
    a. Inadequate treatment response, intolerance, or contraindication to **TWO** of the following:
        i. Calcium channel blockers
        ii. Alpha adrenergic receptor blockers

iii. Angiotensin II receptor antagonist

b. Prescriber agrees to counsel and evaluate the patient for sudden loss of vision or hearing associated with this medication

c. **NO** concurrent therapy with **ALL** of the following:
   i. Any nitrates (in any form)
   ii. Another PDE-5 inhibitor
   iii. Guanylate cyclase (GC) stimulators
   iv. Alpha blockers

d. The requested **oral** dose does not exceed 20mg / unit

Tadalafil Powder Only

1. Benign prostatic hyperplasia / hypertrophy (BPH)
   a. Age 18 years of age or older
   b. Actively symptomatic including **ONE or MORE** of the following:
      i. Dribbling at the end of urinating
      ii. Inability to urinate (urinary retention)
      iii. Incomplete emptying of bladder
      iv. Incontinence
      v. Nocturia – needing to urinate two or more times per night
      vi. Pain with urination or bloody urine
      vii. Slowed or delayed start of the urinary stream
      viii. Straining to urinate
      ix. Strong and sudden urge to urinate
      x. Weak urine stream
   c. Treatment failure or clinically significant adverse reaction to **ONE** of the following:
      i. Alpha blocker
      ii. 5-alpha reductase inhibitor
   d. **NO** concurrent therapy with **ALL** of the following:
      i. Any nitrates (in any form)
      ii. Another PDE-5 inhibitor
      iii. Guanylate cyclase (GC) stimulators
   e. The requested **oral** dose does not exceed 5 mg / unit

AND ALL of the following for **ALL** powders and **ALL** indications:

1. **NOT** being used for erectile or sexual dysfunction
2. The requested strength is **NOT** commercially available
3. The requested dosage form is **NOT** being used topically

Prior – Approval *Renewal* Requirements

Diagnoses

Patient must have **ONE** of the following

Sildenafil and Tadalafil Powders

1. Pulmonary arterial hypertension (PAH) – WHO Group I
    a. Symptoms have improved or stabilized
    b. Prescriber agrees to counsel and evaluate the patient for sudden loss of vision or hearing associated with this medication
    c. **NO** concurrent therapy with **ALL** of the following:
        i. Any nitrates (in any form)
        ii. Another PDE-5 inhibitor
        iii. Guanylate cyclase (GC) stimulators
        iv. Alpha blockers
    d. **Tadalafil powder only**: **NO** severe hepatic impairment (Child-Pugh Class C) **AND NO** severe renal impairment (creatinine clearance <30 mL/min)
    e. The requested **oral** dose does not exceed 20mg / unit

Sildenafil Powder Only

1. Raynaud's syndrome
    a. Symptoms have improved or stabilized
    b. Prescriber agrees to counsel and evaluate the patient for sudden loss of vision or hearing associated with this medication
    c. **NO** concurrent therapy with **ALL** of the following:
        i. Any nitrates (in any form)
        ii. Another PDE-5 inhibitor
        iii. Guanylate cyclase (GC) stimulators
        iv. Alpha blockers
    d. The requested **oral** dose does not exceed 20mg / unit

Tadalafil Powder Only

1. Benign prostatic hyperplasia / hypertrophy (BPH)
    a. Age 18 years of age or older
    b. Improvement in urinary symptoms
    c. **NO** concurrent therapy with **ALL** of the following:
        i. Any nitrates (in any form)
        ii. Another PDE-5 inhibitor
        iii. Guanylate cyclase (GC) stimulators
    d. The requested **oral** dose does not exceed 5 mg / unit

AND ALL of the following for **ALL** powders and **ALL** indications:

1. **NOT** being used for erectile or sexual dysfunction
2. The requested strength is **NOT** commercially available
3. The requested dosage form is **NOT** being used topically

Policy Guidelines

Pre – PA Allowance

None

Prior – Approval Limits

Duration 2 years for PAH and Raynaud's syndrome
12 months for BPH

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Sildenafil and tadalafil are marketed as Revatio and Adcirca for pulmonary arterial hypertension. Revatio and Adcirca received approval for treatment of pulmonary arterial hypertension (PAH) which is classified by WHO as Group 1. 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. 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 (1-4).

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

1. Revatio [package insert]. New York, NY. Pfizer Inc.; January 2023.
2. Adcirca [package insert]. Indianapolis, IN: Eli Lilly and Company; September 2020.
3. Cialis [package Insert]. Indianapolis, IN: Eli Lilly and Company; June 2020.
4. Viagra [package Insert]. New York, NY. Pfizer Inc.; December 2017.
5. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll* Cardiol. 2013; 62:034-841.
6. 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
7. Roland Fries, Kaveh Shariat, Hubertus von Wilmowsky and Michael Böhm. Sildenafil in the Treatment of Raynaud's Phenomenon Resistant to Vasodilatory Therapy. *Circulation.* 2005 : 2980-2985
8. Ross RD, Bollinger RO, Pinsky WW. Grading the severity of congestive heart failure in infants. Pediatr Cardiol. 1992;13:72–5.
9. 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.

Policy History

Date	Action
December 2013	New addition to PA
December 2013	Annual editorial review
December 2014	Annual editorial review and reference update Addition of no concurrent (dual) therapy with PDE-5 inhibitors
December 2015	Annual review Annual editorial review and reference update
September 2016	Removal of NYHA class IV symptoms, addition of no concurrent therapy with riociguat, addition of therapy resistant Raynaud's syndrome Policy number change from 5.06.15 to 5.40.23
September 2017	Annual editorial review
January 2018	Addition of Tadalafil powder and change in renewal duration from 12 to 24 months
March 2018	Annual review
September 2019	Annual review and reference update
September 2020	Annual review and reference update

September 2021	Annual editorial review and reference update. Reorganized the criteria to clarify which powder is approvable for each indication. Added “not being used for erectile or sexual dysfunction” for all powders, and added “The requested oral dose does not exceed 5mg/unit” under tadalafil powder for BPH
December 2021	Annual editorial review. Revised requirements and approval durations so that they matched their tablet counterpart (i.e., Revatio, Adcirca, Cialis)
September 2022	Annual review
December 2022	Annual review
May 2022	Per FEP, removed male gender requirement
June 2023	Annual editorial review. Added requirement of no dual therapy with another PDE5 inhibitor to tadalafil powder for BPH
September 2023	Annual review
March 2024	Annual review
September 2024	Annual editorial review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 8, 2024 and is effective on October 1, 2024.