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Section:	Prescription Drugs	**Effective Date:**	October 1, 2024
Subsection:	Cardiovascular Agents	**Original Policy Date:**	November 1, 2009
Subject:	Revatio Liqrev	**Page:**	1 of 9

Last Review Date: September 6, 2024

Revatio Liqrev

Description

Revatio, Liqrev (sildenafil)

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)

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, 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/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 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 (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. Sidenafil 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 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).

Related policies

Adcirca, Adempas, Flolan/Veletri, Letairis, Opsumit, Opsynvi, Orenitram, PDE5 Inhibitor powders, Remodulin, 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.

Revatio/Liqrev may be considered **medically necessary** if the conditions indicated below are met.

Revatio/Liqrev may be considered **investigational** for all other indications.

Prior-Approval Requirements

Diagnoses

Patient must have **ONE** of the following

1. Pulmonary Arterial Hypertension - WHO Group I
    a. NYHA functional classification of physical activity - Class II or III
    b. Prescribed by or recommended by a cardiologist or pulmonologist

2. 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

AND NONE of the following:

1. Concurrent therapy with any nitrates (in any form)
2. Concurrent therapy with another phosphodiesterase 5 (PDE5) inhibitor
3. Concurrent therapy with guanylate cyclase (GC) stimulators
4. Concurrent therapy with alpha blockers

AND ALL of the following:

1. Prescriber agrees to counsel and evaluate the patient for sudden loss of vision or hearing associated with this medication
2. **Brand Revatio only:** Patient **MUST** have tried the preferred product (generic Revatio: sildenafil) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

Prior – Approval *Renewal* Requirements

Diagnoses

Patient must have **ONE** of the following

1. Pulmonary Arterial Hypertension - WHO Group I
2. Raynaud's syndrome

AND NONE of the following:

1. Concurrent therapy with any nitrates (in any form)
2. Concurrent therapy with another phosphodiesterase 5 (PDE5) inhibitor
3. Concurrent therapy with guanylate cyclase (GC) stimulators
4. Concurrent therapy with alpha blockers

AND ALL of the following:

1. Symptoms have improved or stabilized
2. Prescriber agrees to counsel and evaluate the patient for sudden loss of vision or hearing associated with this medication
3. **Brand Revatio only:** Patient **MUST** have tried the preferred product (generic Revatio: sildenafil) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Duration 2 years

Prior – Approval *Renewal* Limits

Same as above

Rationale

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.

References

1. Revatio [package insert]. New York, NY: Pfizer Inc; January 2023.
2. Liqrev [package insert]. Farmville, NC: CMP Pharma, Inc.; April 2023.
3. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll* Cardiol. 2013; 62:034-841.
4. 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.
5. Ross RD, Bollinger RO, Pinsky WW. Grading the severity of congestive heart failure in infants. Pediatr Cardiol. 1992;13:72–5.
6. 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.
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. 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.

Policy History

Date	Action
November 2009	The FDA has approved Revatio (sildenafil, from Pfizer) injection, an intravenous phosphodiesterase-5 (PDE-5) inhibitor, for the treatment of adults

	with pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and delay clinical worsening. Revatio injection is for the continued treatment of patients with PAH who are currently prescribed Revatio tablets but who are temporarily unable to take oral medication. Revatio injection will be available in a single-use vial. Revatio tablets are already available in 20mg dosage strength.
December 2009	Both PDE5 inhibitors are indicated for the treatment of PAH WHO group 1, NYHA class II, III, or IV. Patients taking tadalafil or sildenafil may see an improvement in NYHA class that could prevent them from qualifying for prior approval renewal. Studies show evidence of improvements in functional class (NYHA class), usually one class jump only; such as from class II to class I. Renewal requirements have been modified to allow continuation of therapy for patients who were previously NYHA Class II for tadalafil or sildenafil, but whose condition has improved on therapy to NYHA Class I.
September 2012	The U.S. Food and Drug Administration (FDA) recommends that Revatio (sildenafil) not be prescribed to children (ages 1 through 17) for pulmonary arterial hypertension (PAH; high pressure in the blood vessels leading to the lungs).
March 2013	Annual editorial review and reference update
March 2014	Annual review
September 2014	Line addition of Revatio oral recon suspension
March 2015	Annual editorial review and reference update Addition of no concurrent therapy with phosphodiesterase inhibitors. Removal of Nitrate examples
April 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 5.16.06 to 5.40.11
June 2016	Annual editorial review and reference update
September 2017	Annual review and reference update
November 2017	Addition of Children's NYHA functional class chart
March 2018	Annual review
September 2019	Annual editorial review and reference update. Changed approval duration from lifetime to 2 years
March 2020	Annual review. Revised background section and added requirements of no concomitant therapy with alpha blockers and patient will be evaluated for sudden loss of vision or hearing. Also added initial requirement of prescribed by or recommended by a cardiologist or pulmonologist per SME
December 2020	Annual review and reference update. Added requirement that brand Revatio has to t/f the preferred product sildenafil
September 2021	Annual review
December 2021	Annual editorial review. Changed requirement from "no dual therapy with riociguat" to "no dual therapy with guanylate cyclase (GC) stimulators"
September 2022	Annual review

December 2022	Annual review
June 2023	Updated regulatory status section per PI update. Added Liqrev oral suspension to policy
September 2023	Annual review
March 2024	Annual review
September 2024	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 6, 2024 and is effective on October 1, 2024.