Medical Drug Clinical Criteria

Subject:	Winrevair (sotatercept-csrk)		
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Overview

This document addresses the use of Winrevair (sotatercept-csrk), an activin signaling inhibitor approved by the Food and Drug Administration (FDA) for the treatment of adults with pulmonary arterial hypertension (PAH) [World Health Organization (WHO) Group 1] to increase exercise capacity, improve WHO functional class and reduce the risk of clinical worsening events. Winrevair is administered subcutaneously every three weeks. The starting dose is 0.3 mg/kg and the target dose is 0.7 mg/kg.

Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by sustained elevations of the mean pulmonary artery pressure (mPAP), thickening of the pulmonary arteries and narrowing of the blood vessels. As the disease progresses, the right side of the heart becomes enlarged and may fail. Right heart catheterization is essential to confirm a diagnosis. PAH is defined by the 2009 American College of Cardiology Foundation (McLaughlin 2009) and the American Heart Association (ACCF/AHA) Expert Consensus Document on Pulmonary Hypertension and by updated specialty society guidelines for adults and children (2013 ACCF Hoeper; 2013 ACCF Ivy; 2015 AHA/ATS Abman) as all of the following:

1. Mean pulmonary artery pressure (mPAP) greater than or equal to 25 mm Hg at rest;
2. Pulmonary capillary wedge pressure (PCWP), mean pulmonary artery wedge pressure (PAWP), left atrial pressure or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mm Hg;
3. Pulmonary vascular resistance (PVR) greater than 3 Wood units.

Agents approved by the FDA to treat PAH were studied in populations meeting these right heart catheterization diagnostic parameters. The 6th World Symposium on Pulmonary Hypertension (Simonneau 2019) proposed updating the definition of pulmonary hypertension to include individuals with a mPAP greater than 20 mm Hg and a PVR greater than 2 Wood units. The guidance did note that prospective clinical trials would be needed to determine if individuals meeting the expanded PAH definition would benefit from currently approved PAH treatments. The 7th World Symposium (Kovacs 2024) confirmed both the new PAH definition and the need for additional clinical studies in individuals meeting the expanded definition.

Medical management of PAH consists of diuretics, supplemental oxygen, anticoagulants, calcium channel blockers, phosphodiesterase-5 (PDE-5) inhibitors, endothelin receptor antagonists (ERA), soluble guanylate cyclase stimulators, prostacyclin receptor agonists, activin signaling inhibitors and oral, inhaled or infused prostacyclin analogs. There are no direct comparisons between products in the literature, making it difficult to support the use of one drug over another in terms of efficacy. Some safety parameters and administration issues do differ between products. As a result, treatment choices should be individualized. Lung or heart-lung transplantation has been performed in individuals who are refractory to medical management.

In 2019, updated CHEST guidelines on pulmonary arterial hypertension therapy were published (Klinger 2019). The 2019 guidance primarily reaffirms the 2014 CHEST guidance but with a new focus on combination therapy in certain clinical situations. A trial of oral calcium channel blocker therapy is recommended for individuals who demonstrate acute vasoreactivity. The guidance recommends treatment naïve individuals with functional class II and III symptoms initiate therapy with Letairis in combination with Adcirca. If an individual cannot tolerate dual therapy, the guidelines recommend monotherapy with an ERA, PDE-5 inhibitor or a soluble guanylate cyclase stimulator. The guidance recommends initiating therapy with a parenteral prostanoid for individuals with functional class IV symptoms.

In 2024, the 7th World Symposium published a treatment algorithm for pulmonary hypertension (Chin 2024). For low-risk individuals, the guidelines recommend a combination of an ERA and a PDE-5 inhibitor. High-risk individuals require more aggressive strategies including a combination of parenteral prostanoid, ERA and PDE-5 inhibitor. Frequent reassessment of risk is stressed and escalation to three or four drugs in combination is recommended for anyone who is not at low risk. Winrevair is included in the algorithm as an add on option for individuals on dual or triple therapy who remain at intermediate-low risk or higher.

The clinical efficacy of Winrevair was demonstrated in a multicenter, randomized, double-blind, placebo-controlled trial in 323 individuals with pulmonary arterial hypertension who were World Health Organization [WHO] functional class II or III. Right-heart catheterization at baseline was required to show a minimum pulmonary vascular resistance (PVR) of ≥ 400 dynes·sec·cm^{-5} (5 Wood units) and a pulmonary capillary wedge pressure or left ventricular end-diastolic pressure of ≤ 15 mmHg. Participants were required to be on stable background PAH therapy and received Winrevair or placebo as add-on therapy. The primary end point was the change from baseline at week 24 in the 6-minute walk distance. The primary endpoint favored Winrevair over placebo with a difference of 40.8 m (95% CI, 27.5 to 54.1, P<0.001).

Comprehensive Clinical Classification of Pulmonary Hypertension (PH) (CHEST 2019)

1. PAH

1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 *BMPR2*
1.2.2 *ALK-1, ENG, SMAD9, CAV1, KCNK3*
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1'. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1'.1 Idiopathic
1'.2 Heritable
1'.2.1 *EIF2AK4* mutation
1'.2.2 Other mutations
1'.3 Drugs, toxins, and radiation induced
1'.4 Associated with:
1'.4.1 Connective tissue disease
1'.4.2 HIV infection
1". Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension because of left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension because of lung diseases and/or hypoxia
3.1 COPD
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 lung diseases
4. Chronic thromboembolic pulmonary hypertension
4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
4.2.1 Angiosarcoma
4.2.2 Other intravascular tumors
4.2.3 Arteritis
4.2.4 Congenital pulmonary arteries
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy

5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral

WHO Functional Classification of PH (CHEST 2019)

- Class I: No limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
- Class II: Slight limitation of physical activity. Comfortable at rest but ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
- Class III: Marked limitation of physical activity. Comfortable at rest but less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
- Class IV: Inability to carry out any physical activity without symptoms. Dyspnea and/or fatigue may be present at rest and discomfort is increased by any physical activity.

Clinical Criteria

Winrevair (sotatercept-csrk)

Requests for Winrevair (sotatercept-csrk) may be approved if the following criteria are met:

I. Individual has pulmonary arterial hypertension (PAH) [World Health Organization (WHO) Group 1]; **AND**
II. Individual has a right-heart catheterization showing all of the following (Hoeper 2023):
    A. Pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mm Hg;
    B. Pulmonary vascular resistance (PVR) greater than or equal to 5 Wood units; **AND**
III. Individual has WHO functional class II or III symptoms; **AND**
IV. Individual is currently receiving two or more pulmonary arterial hypertension agents from two or more different drug classes [phosphodiesterase-5 (PDE-5) inhibitors, endothelin receptor antagonists (ERA), soluble guanylate cyclase stimulators, prostacyclin receptor agonists, prostacyclin analogs] (Chin 2024); **AND**
V. Individual is requesting Winrevair as add-on therapy to be used in combination with other pulmonary arterial hypertension agents; **AND**
VI. Individual has a platelet count greater than or equal to 50,000/mm^3.

Continuation requests for Winrevair (sotatercept-csrk) may be approved if the following criteria are met:

I. There is clinically significant improvement or stabilization in clinical signs and symptoms of disease (including but not limited to improvement in walk distance, dyspnea and/or functional class); **AND**
II. Individual is using Winrevair as add-on therapy in combination with other pulmonary arterial hypertension agents; **AND**
III. Individual has a platelet count greater than or equal to 50,000/mm^3.

Quantity Limits

Winrevair (sotatercept-csrk) Quantity Limits

Drug	Limit
Winrevair (sotatercept-csrk) 45 mg kit (1 vial per kit)	1 kit per 3 weeks
Winrevair (sotatercept-csrk) 45 mg kit (2 vials per kit)	1 kit per 3 weeks
Winrevair (sotatercept-csrk) 60 mg kit (1 vial per kit)	1 kit per 3 weeks
Winrevair (sotatercept-csrk) 60 mg kit (2 vials per kit)	1 kit per 3 weeks

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J3590	Unclassified biologics (when specified as [Winrevair] (sotatercept-csrk)
C9399	Unclassified drugs or biologicals (when specified as [Winrevair] (sotatercept-csrk)

ICD-10 Diagnosis

I27.0	Primary pulmonary hypertension
!27.21	Secondary pulmonary arterial hypertension

Document History

Revised: 2/21/2025
Document History:

- 2/21/2025 – Annual Review: Add criteria to clarify when Winrevair can be added to combination therapy. Coding Reviewed: Removed all diagnosis pend. Added ICD-10-CM I27.0 and I27.21.
- 4/1/2024 – Select Review: New clinical criteria and quantity limits for Winrevair. Coding Reviewed: Added HCPCS J3590, C9399. All diagnosis pend.

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