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Drug Class Update with New Drug Evaluation: Pulmonary Arterial Hypertension

Date of Review: December 2024

Date of Last Review: October 2021
Dates of Literature Search: 07/01/2021 – 08/29/2024
Generic Name: sotatercept-csrk
Brand Name (Manufacturer): Winrevair (Merck and Co, Inc)
Dossier Received: yes

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this class update is to evaluate new comparative evidence for PAH drugs and evaluate place in therapy of a new drug, sotatercept, approved by the Food and Drug Administration in 2024 for treatment of pulmonary arterial hypertension (PAH).

Plain Language Summary:

- Pulmonary arterial hypertension (PAH) is a condition caused by high blood pressure in the lungs. This high blood pressure can lead to difficulty breathing, heart failure, and death.
- Several medicines can improve symptoms in people with PAH. Professional organizations recommend initial treatment with tadalafil and ambrisentan to improve exercise ability. In people who continue to have symptoms, evidence shows that addition of more than one medicine can decrease risk of worsening symptoms, hospitalization, or death.
- The Food and Drug Administration recently approved a medicine called sotatercept for people who have PAH. Most people who received sotatercept were already on 2 or 3 medicines for pulmonary arterial hypertension. In people with PAH, sotatercept improved exercise ability, symptoms, and clinical events related to worsening disease compared to people who received placebo (or injections without medicine).
- We recommend the Oregon Health Authority pay for sotatercept when Oregon Health Plan members have symptoms of PAH and when they are seeing a lung or heart specialist.

Research Questions:

1. What is the comparative efficacy or effectiveness of therapies for pulmonary hypertension based on exercise capacity, functional status, pulmonary function, hospitalizations, quality of life, or disease progression?
2. What is the comparative safety of therapies for people with pulmonary hypertension?
3. What is the efficacy and safety of sotatercept for the treatment of people with pulmonary hypertension?
4. Are there any subgroups (based on age, gender, race or ethnicity, disease classification or etiology, functional status, or concomitant treatments) that would benefit or be harmed from drugs for pulmonary hypertension?

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Conclusions:

- No new high quality comparative systematic reviews or randomized controlled trials (RCTs) were identified since the last class update.
- In 2023, the Food and Drug Administration (FDA) approved sildenafil to treat PAH in pediatric patients.[1] Approval was based on hemodynamic outcomes in in patients less than 17 years of age and an RCT demonstrating improved mortality in adults with PAH.[1]
- There is low quality evidence from one placebo-controlled RCT, that use of inhaled treprostinil may increase risk of serious adverse events (including exacerbations and acute respiratory failure) in people with chronic obstructive pulmonary disease (COPD) and moderate to severe pulmonary hypertension.[2] Adverse events leading to hospitalization and serious adverse events were more common with treprostinil (25.8%) than placebo (10.3%).[2] Labeling for treprostinil was updated to include warnings for bronchospasm.[3]
- There is no evidence to compare sotatercept to other treatments for pulmonary hypertension.
- In people with PAH and World Health Organization (WHO) functional class II or III symptoms, sotatercept improved exercise capacity and PAH symptoms compared to placebo when added to existing PAH therapy (low quality evidence).[4] The most common types of baseline therapy included triple therapy with an endothelial receptor antagonists (ERA), phosphodiesterase (PDE)-5 inhibitor and injectable prostacyclin (51%) or dual therapy with a PDE-5 inhibitor plus an ERA (23%).[4] Compared to placebo, sotatercept improved 6-minute walking distance (6MWD) at 24 weeks (median difference 40.8 meters; 95% confidence interval [CI] 27.5 to 54.1), WHO functional class improvement (29.4% vs. 13.8%), and time to the first clinical worsening event (hazard ratio [HR] 0.16; 95% CI 0.08 to 0.35).[4] Clinical worsening events occurred in 26.2% of people who received placebo compared to 5.5% of people who received sotatercept over a median enrollment of 33 weeks.[4] The definition for clinical worsening included:
    - rescue therapy with background treatment or increase in the prostacyclin dose by ≥10%,
    - lung or heart–lung transplantation, atrial septostomy, or death,
    - hospitalization (≥24 hours) for PAH, or
    - worsening PAH defined as a decline in WHO functional class and a decrease ≥15% in 6MWD.
- There is insufficient evidence to evaluate long-term safety of sotatercept. Common adverse events included telangiectasia, epistaxis, rash, erythema, diarrhea, headache, and dizziness.[5] Increased hemoglobin levels and thrombocytopenia were more common with sotatercept than placebo. Bleeding events were generally mild, and were more common in older adults (≥65 years of age), people prescribed concomitant prostacyclins or antithrombotic agents, or people with low platelet counts.[5,6] People with abnormal hemoglobin or platelet counts were excluded from clinical studies.
- There are currently no published studies evaluating sotatercept in people with other types of pulmonary hypertension, WHO class IV symptoms, people with moderate-severe comorbid lung conditions, or people with recent cardiac events.

Recommendations:

- Implement prior authorization (PA) criteria for sotatercept to support use as add-on treatment in PAH.
- No PDL changes are recommended based on clinical evidence. After evaluation of costs in executive session, tadalafil tablets were made preferred.

Summary of Prior Reviews and Current Policy

- *Pulmonary arterial hypertension (WHO group 1):* There is limited direct comparative evidence evaluating efficacy and safety of treatments for PAH in this population. The majority of available RCTs are placebo-controlled and evaluate changes in functional status or exercise capacity using the 6MWD. Most studies have not been powered to determine differences in morbidity or mortality. Prior reviews suggest that there are no statistically significant differences in clinical worsening (defined as change in WHO functional class, initiation of treatment with intravenous or subcutaneous prostanoids, all-cause mortality, heart or lung transplant, or atrial septostomy) between monotherapy treatments for treatment-naïve patients with PAH and WHO functional class II or III.[7]

Pooled data based on drug class has suggested that oral phosphodiesterase (PDE)-5 inhibitors and intravenous epoprostenol may be associated with a statistically significant mortality reduction compared to placebo.[7] Sequential (add-on) combination therapy may be considered to slow clinical worsening compared to monotherapy. However, there is little data to guide the duration of initial drug therapy before switching or adding another drug.[7] Oral and inhalation therapies have been considered an appropriate option for class II-IV patients but do not necessarily negate the need for injectable prostanoids. Preferred oral formulations include bosentan and sildenafil. Historically, intravenous epoprostenol had been the treatment of choice in class IV patients based on recommendations from the American College of Chest Physicians and the American College of Cardiology Foundation/American Heart Association and is currently the preferred intravenous formulation.[7,8]

- *Pulmonary hypertension due to left heart disease (WHO group 2):* Evidence remains insufficient for use of targeted therapies in this population.[9]

- *Pulmonary hypertension due to lung disease (WHO group 3):* There is low quality evidence from a single randomized controlled trial (RCT) that use of inhaled treprostinil four times daily has a modest benefit on exercise capacity in patients with pulmonary hypertension due to interstitial lung disease (mean difference in the 6MWD of 31.12 meters; 95% CI 16.85 to 45.39) with no difference in mortality, hospitalizations due to pulmonary hypertension, or quality of life.[10] Ambrisentan and riociguat are contraindicated in people with interstitial lung disease or COPD.

- *Chronic thromboembolic pulmonary hypertension (CTEPH; WHO group 4):* Riociguat is currently the only PAH-specific therapy also FDA-approved for patients with CTEPH. There is moderate strength of evidence that riociguat improved the 6MWD in patients with CTEPH.[11]

Clinical PA criteria is required for all non-preferred products listed in **Appendix 1**. Non-preferred products must be prescribed by a pulmonologist or cardiologist. In patients with PAH (WHO Group 1), oral therapy may be considered for patients with functional class II-IV symptoms. Riociguat may also be approved for patients with chronic thromboembolic PAH (WHO Group 4) and functional class II-IV symptoms. Intravenous therapy may be approved for patients with PAH (WHO Group 1) and functional class III-IV symptoms.

Background:
Pulmonary hypertension is defined as a mean pulmonary arterial pressure of more than 20 mmHg and pulmonary vascular resistance of at least 3 Wood units.[12] Guidelines published in 2022 from the European Respiratory Society suggest pulmonary vascular resistance of at least 2 Wood units may necessitate diagnosis and treatment for pulmonary hypertension.[12,13] Other guidelines have not yet adopted this new definition. Diagnosis requires right heart catheterization to evaluate pulmonary arterial pressure and pulmonary vascular resistance. Pulmonary hypertension is further classified into 5 categories based on etiology. These include pulmonary arterial hypertension (PAH; WHO group 1), pulmonary hypertension due to left heart disease (WHO group 2), pulmonary hypertension due to lung disease and hypoxia (WHO group 3), chronic thromboembolic pulmonary hypertension (CTEPH, WHO group 4) and pulmonary hypertension with an unclear multifactorial cause (WHO group 5) .[12,13] About 1% of people have pulmonary hypertension with incidence increasing with age.[12] Left heart disease and lung disease are the most common causes of pulmonary hypertension.[12] Diagnosis of PAH requires ruling out alternative causes of pulmonary hypertension.

Common signs and symptoms of pulmonary hypertension include dyspnea, fatigue, chest pain, palpitations, syncope, and fluid retention.[12] Symptoms severity is often classified according to the WHO functional class (**Table 1**). The average survival time from diagnosis is about 5-7 years for people with PAH, but prognosis varies based on the underlying etiology and comorbid conditions.[6,12] Multiple factors have been associated with increased risk of mortality for people with PAH including rapid symptom progression, increasing WHO functional status, diminished exercise capacity, right heart failure, and elevated B-type natriuretic peptide (BNP) levels.[12] Common complications of PAH include hemoptysis, right heart failure, arrhythmias, ascites, and pulmonary artery rupture or dissection.[12]

Table 1. WHO functional classes

WHO Class	Description
Class I	No limitations in physical activity; physical activity does not cause symptoms
Class II	Slight limitations in physical activity; ordinary physical activity causes symptoms
Class III	Limitations of physical activity; less than ordinary activity causes symptoms
Class IV	Symptoms at rest and/or with any physical activity

Each type of pulmonary hypertension has a unique etiology, pathology and management strategy. Current standard of care for patients with PAH (WHO group 1) includes oral calcium channel blockers for patients who respond to acute vasoreactive testing (approximately 10% of patients). Other supportive care includes diuretics for fluid retention, digoxin to improve cardiac output and slow ventricular rate, anticoagulants to decrease risk for thromboembolic events, oxygen, supervised physical activity, and rehabilitation.[12,13] Targeted therapies are FDA-approved for PAH (WHO group 1), CTEPH (WHO group 4) and pulmonary hypertension due to interstitial lung disease (WHO group 3). PAH-specific therapies are generally considered for patients with functional class II-IV symptoms. Current PAH-specific treatment options include the following drugs:

- Phosphodiesterase (PDE)-5 inhibitors: sildenafil and tadalafil
- Endothelial receptor antagonists (ERAs): bosentan, macitentan, and ambrisentan
- Soluble guanylate cyclase stimulators: riociguat (also indicated for CTEPH; WHO group 4)
- Prostacyclin receptor agonists: selexipag
- Prostanoids: epoprostenol (intravenous), treprostinil (oral, subcutaneous, intravenous); treprostinil (inhaled, also indicated for WHO group 3), and iloprost (inhaled)
- Activin receptor protein: sotatercept

Guidelines for management of PAH published in 2019 recommend initial combination treatment with tadalafil and ambrisentan to improve 6MWD in treatment-naïve patients with WHO functional class II and III symptoms who are not candidates for calcium channel blockers (weak recommendation, moderate quality evidence).[14] If patients are unable to tolerate combination treatment then monotherapy with an ERA, PDE-5 inhibitor, or soluble guanylate cyclase inhibitor is suggested.[14] The following treatments had the most evidence to support use:

- Ambrisentan to improve 6MWD in people with WHO class II or III symptoms (strong recommendation; low quality evidence).
- Sildenafil to improve 6MWD in people with WHO class II or III symptoms (strong recommendation; low quality evidence).
- Bosentan to improve 6MWD (strong recommendation; moderate quality evidence) and decrease hospitalizations (weak recommendation; low quality evidence) in people with WHO class III symptoms.

Evidence-based recommendations were also included for subsequent or add-on treatment for the following groups:

- For people with WHO class III symptoms with evidence of disease progression or markers of poor clinical prognosis despite initial treatment with an ERA or PDE-5 inhibitor, consider addition of a parenteral or inhaled prostanoid. There is evidence to support addition of inhaled treprostinil to improve 6MWD (weak recommendation; low quality evidence).[14]
- In people with class III or IV symptoms despite PAH monotherapy, addition of a second class of therapy is recommended to improve exercise capacity. There is the most evidence support addition of inhaled treprostinil in people with class III or IV on stable doses of an ERA or PDE-5 inhibitor (strong recommendation; low quality evidence).[14]
- In patients on stable dose of ambrisentan, addition of tadalafil is suggested to improve 6MWD (weak recommendation; low quality evidence).[14]

There was insufficient evidence to provide evidence-based recommendations for other groups or outcomes. Other guideline recommendations were classified as ungraded consensus-based statements to indicate uncertainty in the evidence and reliance on expert opinion.[14]

In people with pulmonary hypertension due to lung diseases or hypoxia (WHO group 3), current guidelines recommend treatment of the underlying lung condition and do not generally recommend targeted therapies for pulmonary hypertension.[12] This recommendation is based on limited evidence indicating that targeted therapies including (iloprost, riociguat, and ambrisentan) may not improve symptoms or functional outcomes, and in the case of riociguat and ambrisentan, may be associated with increased risk of adverse events including mortality.[12] Because of this risk, riociguat and ambrisentan are contraindicated in patients with interstitial lung disease.[12] Nebulized treprostinil may be considered to improve exercise capacity in patients with pulmonary hypertension associated with interstitial lung disease based on results from a single phase 3 RCT.[10,13] Treatment effects were generally modest, and there was no difference observed in mortality, quality of life, or hospitalizations due to pulmonary hypertension.[10]

In patients with CTEPH (WHO Group 4), standards of care include supervised cardiopulmonary exercise rehabilitation, supplemental oxygen, diuretics for fluid retention, and lifetime anticoagulants to prevent thromboembolic events. Pulmonary endarterectomy is recommended for surgery-eligible patients, and if successful, may potentially be curative with survival rates of 74 to 89% at 5 years after surgery.[15,16] However, not all patients are eligible for surgery, and the disease either recurs or is refractory to surgery in 5 to 35% of cases.[17] Patients who are not surgical candidates may consider drug therapy, primarily treatment with riociguat to improve exercise intolerance. Riociguat is currently the only PAH-specific therapy also FDA-approved for patients with CTEPH. Current guidelines suggest PAH therapies may be considered for off-label use in patients with inoperable CTEPH.[13,16] However, recommendations are supported by limited evidence such as small RCTs, non-randomized studies, indirect evidence, or lack of clinical outcome data.[13,16]

Goals of therapy for all types of pulmonary hypertension include morbidity and mortality reduction, symptom improvement, and decreased disease progression. Outcomes studied in clinical trials include hemodynamic endpoints, 6MWD, and time to clinical worsening endpoints. The majority of trials have not been designed to evaluate long-term outcomes of mortality or disease progression. 6MWD is often used to evaluate exercise capacity. While poor 6MWD at baseline and rapid decline in 6MWD (>15% over 1 year) may have some prognostic value, improvements of up to 15% change in 6MWD over 1 year have not demonstrated any correlation with mortality reduction or disease progression for patients with PAH.[18] Patients with 6MWD greater than 440 to 500 meters are generally considered to be at low risk for clinical events,[15,19] and minimum clinically important differences (MCID) referenced in the literature range from 21 to 45 m depending on the type and cause of the pulmonary disease.[10,20] Many other scales can be used to evaluate symptom improvement. Common scales which evaluate respiratory symptoms include the Borg dyspnea scale which evaluates dyspnea symptoms on a 0-7 point scale (MCID 1 point)[21] and the St George's Respiratory Questionnaire which evaluates quality of life on a 0-100 point scale (MCID 4 points). The Pulmonary Arterial Hypertension—Symptoms and Impact Questionnaire (PAH-SYMPACT) score is another scale used in clinical trials to evaluate PAH-related symptoms and impact of PAH on daily life.[22] It is a patient-reported scale that includes oxygen utilization, 11 questions related to PAH symptoms, and 11 questions related to physical, cognitive, and functional impacts.[22] A MCID for the PAH-SYMPACT score has not been established. Often clinical worsening is defined as a composite endpoint which may include a variety of outcomes such as change in WHO functional class, initiation of treatment with intravenous or subcutaneous prostanoids, hospitalization, all-cause mortality, heart or lung transplant, or atrial septostomy.[23]

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs,

the Canadian Agency for Drugs and Technologies in Health (CADTH), the Oregon Mental Health Clinical Advisory Group (MHCAG), and the Scottish Intercollegiate Guidelines Network (SIGN) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
No new high quality systematic reviews were identified.

After review, 27 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
No new high-quality guidelines were identified.

After review, 3 guidelines were excluded due to poor quality.[13,24,25]

New Formulations or Indications:
In March 2023, sildenafil was FDA-approved for PAH in pediatric patients to improve exercise ability and pulmonary hemodynamics.[1] Sildenafil was previously approved in adult with PAH to improve exercise capacity and delay clinical worsening. Approval was based upon studies of efficacy in adults and 2 RCTs evaluating data in pediatric members. The first RCT randomized 234 patients 1-17 years of age who had PAH to sildenafil monotherapy (3 doses) or placebo.[1] About 32% of patients had WHO functional class I symptoms, 51% had class II symptoms, and 15% had class III symptoms.[1] The most common etiologies were idiopathic PAH (33%) and congenital heart disease (27%).[1] The primary endpoint was percent change in the maximum volume of oxygen consumed (PVO_{2peak}) after 16 weeks and was performed in participants at least 7 years of age who were able to perform the test (45% of people).[1] People treated with sildenafil had improved VO_{2peak} (range 6% to 13% across doses) compared to placebo (0.5%; difference 8%; 95% CI -0.2 to 16%; p=0.056).[1] Compared to placebo, other hemodynamic endpoints (pulmonary vascular resistance and mean pulmonary arterial pressure) were improved in people randomized to medium or high dose sildenafil. Secondary outcomes included WHO functional class change and quality of life measures.[1] A dose response was observed for change in WHO functional class, and differences were statistically significant for patients prescribed high dose sildenafil compared to placebo (OR 4.5; 95% CI 1.6 to 13.1).[26] Participants could subsequently enroll in an extension study to evaluate long-term efficacy and comparative doses of sildenafil. The median duration of treatment in the extension study was 4.6 years.[1] For people over 20 kg, survival at 3 years was 94%, 93% and 85% in the low, medium and high dose sildenafil groups, respectively.[1] A subsequent study of high (80 mg three times daily [TID]), medium (20 mg TID), and low (5 mg TID) dose sildenafil in adults with PAH was conducted to further examine risk of mortality based on dose.[1] The study was discontinued early because an interim analysis confirmed that 80 mg TID met non-inferiority criteria for mortality compared to the low dose (5 mg TID) group (HR 0.51; 99.7% CI 0.22 to 1.21).[1] Survival estimates at 3 years were 66%, 79% and 85% for the 5 mg, 20 mg and 80 mg TID groups.[1] Secondary outcomes included time to first event of clinical worsening and the 6MWD at 6 and 12 months. Patients randomized to 80 mg TID had fewer clinical worsening events compared to patients receiving 5 mg TID (40% vs. 22%; HR 0.44; 99.7% CI 0.22 to 0.89).[1]

In May 2022, a new formulation of treprostinil was approved as a dry powder inhaler for PAH and pulmonary hypertension related to interstitial lung disease.[27] Treprostinil was previously FDA-approval as an inhaled solution. Approval was primarily based on a 3-week open-label, pharmacokinetic study in which patients were transitioned from the solution to the dry powder inhaler (n=51).[27] Pharmacokinetic testing demonstrated similar AUCs upon comparison of the dry powder inhaler and inhaled solution.[27] Adverse events observed in the trial were consistent with the known safety profile of treprostinil.[27]

In March 2024, a new combination tablet including macitentan and tadalafil was approved by the FDA for people with PAH and WHO functional class II or III.[28] In a double-blind, multicenter RCT, pulmonary vascular resistance was reduced with combination treatment compared to monotherapy with either macitentan (RR 0.71; 95% confidence level 0.61 to 0.82) or tadalafil (relative risk [RR] 0.72; 95% CL 0.64 to 0.80).[28] Prior studies have demonstrated that tadalafil monotherapy can improve 6MWD and macitentan monotherapy can reduce risk of clinical worsening or hospitalization in people with PAH.[28]

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month/Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Treprostinil[3]	Tyvaso	5/2022	Warnings/Precautions	Treprostinil is associated with bronchospasm. People with asthma or COPD may have increased risk.[3] A placebo-controlled, crossover, RCT evaluated efficacy and safety of inhaled treprostinil in people with COPD, forced expiratory volume in 1 second (FEV_1) less than 80%, and moderate to severe pulmonary hypertension (n=76).[2] The primary endpoint was change in 6MWD after 12 weeks. The study was terminated early after an interim safety analysis identified that people who received inhaled treprostinil had an increased rate of serious adverse events and no difference in 6MWD compared to placebo.[2] Adverse events leading to hospitalization and serious adverse events (SAEs) were more common with treprostinil (17/66; 25.8%) than placebo (6/58; 10.3%).[2] SAEs included COPD exacerbations and acute respiratory failure.[2] Six deaths occurred during the study (5 of which were in people randomized to treprostinil).[2] Fatigue, chest discomfort, dyspnea and cough were more common with treatment than placebo.[2]
Riociguat[29]	Adempas	9/2021	Contraindications	Riociguat is contraindicated with concomitant use of other soluble guanylate cyclase stimulators.

Randomized Controlled Trials:

A total of 138 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION:

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Sotatercept is a fusion protein which inhibits activin signaling. Activin in a type of transforming growth factor β (TGF-β) molecule that promotes cell proliferation and anti-apoptotic signaling.[4] Endothelial and smooth muscle cell proliferation resulting in pulmonary vasculature remodeling is thought to be a primary driver of pulmonary arterial hypertension.[4] Sotatercept is able to bind TGF-β signaling molecules and improve pulmonary vasculature remodeling.[4]

The FDA approved sotatercept based on evidence from one phase 3, double-blind placebo-controlled, RCT evaluating use in people with PAH.[4] Supplementary information was also available from phase 2 studies. People were randomized to placebo or sotatercept at a maintenance dose of 0.7 mg/kg subcutaneously every 3 weeks.[4] Dose reduction due to adverse events was permitted. After 24 weeks, participants could elect to continue double-blind treatment for up to 72 weeks or until the final patient completed the 24 week period.[4] The primary outcome evaluated in the phase 3 trial was change in exercise capacity after 24 weeks evaluated with the 6MWD.[4] Relevant clinical secondary outcomes included change in WHO functional class at 24 weeks, time to the first occurrence of death or non-fatal clinical worsening event, and change in PAH symptoms evaluated with the PAH-SYMPACT score. Clinical worsening events were adjudicated by an independent committee unaware of treatment groups and defined as worsening-related listing for lung or heart–lung transplantation, initiation or rescue therapy with an approved background treatment or increase in the prostacyclin dose by ≥10%, atrial septostomy, hospitalization (≥24 hours) for worsening of pulmonary arterial hypertension, or worsening of pulmonary arterial hypertension relative to baseline as defined by both a worsened WHO functional class and a decrease in 6-minute walk distance by ≥15% (confirmed by two tests ≥4 hours but ≤1 week apart).[4]

People included in the trial had PAH, WHO functional class II or III, and were on a stable dose of baseline PAH treatment.[4] The average 6MWD was 401 meters and 51% of people had WHO functional class III.[4] Most people were on treatment with either 2 or 3 targeted PAH therapies (34.7% and 61.3% of people, respectively).[4] The most common types of baseline therapy included:[4]

- triple therapy with ERA, PDE-5 inhibitor and injectable prostacyclin (51%),
- dual therapy with a PDE-5 inhibitor plus an ERA (23%), and
- triple therapy with ERA, injectable prostacyclin and a soluble guanylate cyclase stimulator (11%)

The median age of participants was 48 years and the median time since diagnosis was 8.8 years for participants in the trial.[4] Compared to data from registry studies of people with PAH, this population may be younger and have a longer time since diagnosis.[4] Information from registry studies indicates that the median survival time ranges from 5 to 7 years after diagnosis.[4] People were excluded from the trial if they had other types of pulmonary hypertension (WHO groups 2-5), forced vital capacity (FVC) less than 60% of predicted, or comorbid heart or lung diseases that can be common causes of WHO group 2 or 3 pulmonary hypertension (such as cardiomyopathy, recent coronary artery disease events, left ventricular ejection fraction <45%, untreated obstructive sleep apnea or moderate-severe interstitial lung disease).[4] People with recent stroke, elevated blood pressure, elevated hemoglobin levels, or decreased platelet counts less than $50x10^9$ cells/L were also excluded.

At 24 weeks, the median improvement in the 6MWD was 34.4 m (95% CI 33.0 to 35.5) for people treated with sotatercept compared to 1.0 m (95% CI −0.3 to 3.5) in people treated with placebo (median difference 40.8 m; 95% CI 27.5 to 54.1). WHO functional class improved in more people treated with sotatercept (29.4%, 95% CI 2.6 to 37.1) compared to placebo (13.8%, 95% CI 8.9 to 20.2).[4] The composite endpoint of time death or the first clinical worsening event was improved with sotatercept compared to placebo (HR 0.16; 95% CI 0.08 to 0.35).[4] Over a median enrollment of 33 weeks, events occurred in 26.2% of people who received placebo compared to 5.5% of people who received sotatercept.[4] The components of the composite endpoint were generally more common with placebo than sotatercept and included:

- initiation of rescue therapy for PAH or increase in prostacyclin dose by at least 10% (10.6% with placebo vs. 1.2% with sotatercept)
- worsening of pulmonary hypertension (9.4% with placebo vs. 2.5% with sotatercept)
- Death as a first event in the follow up period (3.8% with placebo vs. 1.2% with sotatercept)
- PAH-related hospitalization (4.4% with placebo vs. 0% with sotatercept).[4]

The study was not powered to detect differences in individual components of the composite endpoint including death or hospitalization. The most common cause of death was cardiac disorders.[4] The PAH-SYMPACT physical impacts domain and cardiopulmonary impacts domain scores were improved with sotatercept compared to placebo, but there was no difference in the cognitive/emotional impacts domain score.[4] Differences were generally small and of unclear clinical significance as MCIDs have not been established for this scale.[4]

Pre-specified subgroup analyses generally showed similar direction of effect for various populations based on geographic location, sex, PAH etiology, baseline PAH treatment, WHO functional class, and baseline pulmonary vascular resistance.

Results were generally consistent with the multicenter, phase 2 PULSAR trial which compared sotatercept to placebo in 106 people who were on established PAH therapy.[30] Clinical outcomes studied in this trial included change in the 6MWD, change in WHO functional class, clinical worsening, and quality of life using the 36-item short-form health survey (SF-36) over 24 weeks.[30] Enrolled participants were mostly female (79%), had an average age of 50 years, and had WHO functional class II or III.[30] Etiology of PAH was primarily idiopathic (57%), associated with connective-tissue disease (20%) or heritable (14%).[30] Most participants were on triple (57%) or double therapy (34%) with PAH drugs and 39% were prescribed an intravenous prostacyclin. Compared to placebo, patients treated with sotatercept had improved average 6MWD (53 vs. 29 meters; MD 24.9; 95% CI 3.1 to 46.6).[30] Statistical analysis was not reported for other clinical outcomes, but the study was not powered to detect differences between groups for these outcomes.[30]

Limitations

The trial used adequate randomization methods, but there were differences in PAH etiology and time since diagnosis between groups.[4] Comorbid conditions were also slightly more common in the placebo group than the treatment group including coronary heart disease (7.5% vs. 3.1%), obesity (9.4% vs. 6.1%) and prior pulmonary embolism (5% vs. 3.5%).[4] The impact of these differences on outcomes in this trial is unclear. Differences in adverse events may have led to unblinding during the trial, resulting in increased risk of performance and detection bias. Of people enrolled in the study, 89% identified as White and 79% identified as female.[4] Non-White races were underrepresented in the study. It is not known if PAH prevalence differs based on race, and it is estimated that PAH is 1.5 to 3 times more common in females than males.[4]

Sotatercept has not been studied as monotherapy in PAH or in other types of pulmonary hypertension. There is currently insufficient evidence to evaluate efficacy and safety in people with severe disease (e.g., WHO functional class IV symptoms, moderate-severe lung disease, or recent heart disease) as these populations were excluded from clinical trials. There is no evidence evaluating sotatercept in people who do not have functional impairment (WHO class I symptoms). People were also required to have a pulmonary vascular resistance of at least 5 Wood units to be included in the trial whereas diagnosis of PAH only

requires a pulmonary vascular resistance over 2 or 3 Wood units (depending on the guideline). There are ongoing studies to evaluate sotatercept in people newly diagnosed with PAH and people with WHO class III or IV symptoms who are at increased risk for disease progression or mortality (NCT04811092 and NCT04896008).[31,32]

The phase 3 trial was not powered to detect differences in the individual components of the composite endpoint such as hospitalization and mortality. Trials of sotatercept have been relatively short for a chronic condition, but demonstrate durability of therapy over 1 to 2 years.[4,33] Long-term safety and efficacy remains unknown.

Clinical Safety:
Adverse events observed in clinical trials included epistaxis and telangiectasia, rash and erythema, headache, dizziness, diarrhea, increased, and hematologic abnormalities (**Table 3**). Small increases in blood pressure were also observed after 24 weeks of treatment (mean change of 2.2/4.9 mmHg vs. -1.6/-0.6 mmHg with placebo).[5] In clinical trials, discontinuations related to adverse events were more common with placebo (7%) than sotatercept (4%).[5] In the placebo group, the most common adverse events leading to treatment discontinuation were cardiac disorders and worsening of PAH.[4] Bleeding events (e.g., epistaxis, hemoptysis and intracranial hemorrhage) were the only treatment-emergent adverse event leading to discontinuation that were more common with sotatercept than placebo.[6] Bacterial infections were more common with sotatercept compared to placebo (26% vs. 16%).[6] Infections were more common in people prescribed prostacyclin infusion (35% vs. 14%) and with no difference in infection rates for people who were not on prostacyclin infusion therapy.[6] Common infections included catheter site infections, cellulitis, urinary tract infections, and cystitis.

Table 3. Common adverse events in the phase 3 trial which occurred in >10% of people and more common than placebo[5]

Adverse event	Sotatercept (n=160)	Placebo (n=163)
Hemoglobin > ULN	87 (53%)	23 (14%)
Platelets < LLN	40 (25%)	26 (16%)
Headache	40 (24.5%)	28 (17.5%)
Epistaxis	36 (22.1%)	3 (1.9%)
Rash	33 (20.2%)	13 (8.1%)
Telangiectasia	27 (16.6%)	7 (4.4%)
Diarrhea	25 (15.3%)	16 (10.0%)
Dizziness	24 (14.7%)	10 (6.2%)
Erythema	22 (13.5%)	5 (3.1%)

Abbreviations: LLN = lower limit of normal; ULN = upper limit of normal

Labeling for sotatercept includes warnings for hematologic adverse events such as increased hemoglobin levels, severe thrombocytopenia, and serious bleeding.[5] Elevated hemoglobin levels may increase the risk for thromboembolic events. Elevated hemoglobin levels occurred in 53% of people randomized to sotatercept compared to 14% receiving placebo. Twenty-one percent of people had dose changes related to hemoglobin levels, and hemoglobin levels of more than 2 g/dL above the upper limit of normal were observed in about 15% of patients.[5] In the phase 3 study, thromboembolic events occurred at similar rates with sotatercept (6%) and placebo (4%).[6]

Platelet counts below the lower limit of normal were also more common with sotatercept than placebo (25% vs. 16%). Severe thrombocytopenia less than $50x10^9$ cells/L occurred in 3% of patients, and serious bleeding was more common with treatment (4% vs. 1% with placebo).[5] Bleeding events were generally mild (most commonly epistaxis) and were more common in older patients (≥65 years of age), people prescribed concomitant prostacyclins or antithrombotic agents, or people with low platelet counts. Patients with elevated hemoglobin levels or low platelet counts were generally excluded from clinical studies. Monitoring hemoglobin and platelet levels is recommended prior to the first 5 doses of treatment and periodically thereafter.[5] Delays or reductions in dose are recommended for clinically relevant changes in hemoglobin or platelet levels.

Other warnings for sotatercept include risk for embryo-fetal toxicity and impaired fertility.[5] In animal studies, use of sotatercept resulted in embryo-fetal mortality, growth changes, and structural variations when exposed to doses approximately equal to 0.6 to 4-times the recommended human dose.[5] Use of birth control is recommended during treatment and for 4 months after the final dose.[5] Animal studies also indicate that sotatercept may impair both male and female fertility.[5] Post-marketing requirements include an observational study to assess maternal complications and infant outcomes with incidental sotatercept exposure during pregnancy.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Mortality
2) Hospitalizations
3) WHO functional status
4) Exercise capacity
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Change in 6MWD

Table 4. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Sotatercept is a fusion protein and an activin signaling inhibitor. It binds to activin A and other TGF-beta superfamily ligands to improve vascular proliferation of the endothelial and smooth muscle cells. In animal models, these changes resulted in thinner blood vessel walls, partial reversal of right ventricular remodeling and improved hemodynamics.
Oral Bioavailability	NA; after subcutaneous administration the absolute bioavailability was 66%
Distribution and Protein Binding	Volume of distribution is approximately 5.3L at steady state. Protein binding not reported.
Elimination	Clearance of 0.18 L/day
Half-Life	24 days
Metabolism	Metabolized into small peptides by catabolic pathways

Abbreviations: L = liters; NA = not applicable; TGF = transforming growth factor

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes (AEs at data cut-off date)	ARR/ NNH	Risk of Bias/ Applicability
1.Hoeper, et al.[4] MC, DB, PC, phase 3, RCT NCT04576988 STELLAR trial	1. Sotatercept 0.3 mg/kg for first dose; maintenance dose of 0.7 mg/kg SC every 3 weeks 2. Placebo Dose reduction permitted for AE (hemoglobin, platelets and telangiectasia) 24 weeks with option to continue DB treatment up to 72 weeks or until the final patient completed the 24 week period	<u>Demographics</u>: - Female (79%) - Mean age: 48 years - White: 89% - BMI ≥ 30 kg/m^2: 23% - Time since diagnosis: 8.8 years - PAH Type Idiopathic: 58.5% Heritable 18.3% Connective-tissue disease: 14.9% - WHO functional class II: 48.6% III: 51.4% - PAH therapy Prostacyclin IV:39.9% Double therapy: 34.7% Triple therapy:61.3% - 6MWD: 401 m <u>Key Inclusion Criteria</u>: - PAH (idiopathic, heritable, drug-induced, connective-tissue disease associated, or after shunt correction) - WHO functional class II or III - Stable PAH treatment - PVR ≥ 5 wood units (400 dyn·sec·cm^{-5}) - Pulmonary capillary wedge pressure ≤ 15 mmHg - 6MWD of 150-500 m (2 values within 15% of each other) <u>Key Exclusion Criteria</u>: - PH related to other etiologies (WHO groups 2-5) - FVC < 60% predicted - Moderate-severe interstitial lung disease or untreated OSA - Heart disease (h/o cardiomyopathy, recent	<u>ITT</u>: 1. 163 2. 160 <u>PP</u>: 1. 159 2. 148 <u>Attrition at 24 weeks</u>: 1. 4 (2.4%) 2. 12 (7.5%) <u>Attrition at study cut-off date: *</u> 1. 150 (92%) 2. 112 (70%) *Primary reason for attrition was clinical worsening events	<u>Primary Endpoint</u>: Median change in 6MWD at 24 weeks 1. 34.4m (95% CI 33.0 to 35.5) 2. 1.0 m (95% CI -0.3 to 3.5) Median difference: 40.8 m (95% CI 27.5 to 54.1); p<0.001 <u>Secondary Clinical Endpoints</u>: WHO functional class change 1. 48 (29.4%; 95% CI 22.6 to 37.1) 2. 22 (13.8%, 95% CI 8.9 to 20.2) p<0.001 Time to first nonfatal clinical worsening event* or death (median 32.7 weeks) 1. 9 (5.5%) 2. 42 (26.2%) HR 0.16 (95% CI 0.08 to 0.35)	NA 16%/ 7 21%/ 5	<u>Serious AE</u> 1. 36 (22.1%) 2. 44 (27.5%) Difference: −5.4% (95% CI -14.8 to 4.0) <u>Death (24 weeks)</u> 1. 2 (1.2%) 2. 6 (3.8%) Difference: NR <u>Discontinuation due to AE</u> 1. 6 (3.7%) 2. 11 (6.9%) Difference: −3.2% (95% −8.7 to 1.8) <u>Bleeding events</u> 1. 52 (31.9%) 2. 25 (15.6%) Difference: 16.3% (95% CI 7.1 to 25.4) <u>Thrombocytopenia</u> 1. 14 (8.6%) 2. 5 (3.1%) Difference: 5.5% (95% CI 0.4 to 11.2) MD: 17x10^9 cells/L <u>Increased hemoglobin</u> 1. 10 (6.1%) 2. 0 (0%) Difference: 6.1% (95% CI 3.4 to 10.9) MD: 1.4 g/dL <u>Telangiectasia</u> 1. 23 (14.1%)	NS NR NS 16%/ 7 5.5% /19 6.1% /17	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: UNCLEAR. Adequate randomized and allocation concealment via interactive response technology system. Patients were stratified based on functional class and background PAH therapy. Idiopathic PAH was more common with placebo (66% vs. 51%) and connective tissue disease and heritable PAH was more common with sotatercept. Average age was similar between groups, but the time since diagnosis was about 1 year longer in the sotatercept group compared to placebo (9.2 vs. 8.3 years). <u>Performance Bias</u>: HIGH. Saline used for placebo injections. Potential unblinding related to telangiectasia and hematologic changes. Risk of bias may be largest for effort-based outcomes like the 6MWD and discontinuations due to AEs. <u>Detection Bias</u>: UNCLEAR. Saline used for placebo injections. Potential unblinding related to telangiectasia and hematologic changes. Clinical worsening was evaluated by an independent committee who were unaware of treatment group. <u>Attrition Bias</u>: LOW. Differential attrition between groups with generally more missing data in the placebo group related to death and adverse events (8.1% vs. 3.7% for the 6MWD at 24 weeks). More than 40% of data was missing for symptom assessment using the PAH-SYMPACT score. Analyses conducted in the ITT population. Data were imputed using worst-rank score in the case of death and next worst-rank score in the case of nonfatal clinical worsening. Other missing data was imputed based on the mean from patients with observed data assuming missing at random. Sensitivity analyses evaluating different methods for missing data resulted in a similar magnitude of effect. <u>Reporting Bias</u>: LOW. Hierarchical testing for secondary endpoints. Outcomes reported as pre-specified. <u>Other Bias</u>: UNCLEAR. Funded by Acceleron Pharma who was involved in study design, conduct, and data interpretation. TechData Service performed statistical analyses. **Applicability**: <u>Patient</u>: Races other than white were underrepresented in this study. Median survival is typically 5-7 years from diagnosis.[6] Patients in this study had a median time since diagnosis of 8.8 years. Most applicable to patients with slight limitations in physical activity (WHO functional class II or III).

		coronary disease events, atrial septostomy, LFEF <45%, decompensated heart failure within 30 days, valvular disease, corrected QT interval >500 ms or family history of long QT syndrome or sudden death) - Hemoglobin >ULN - Platelet count <50x10^9 cells/L - CVA within 3 months - Blood pressure >160/100 or systolic <90 mmHg - eGFR <30 mL/min/m^2 - Mild-severe hepatic impairment				2. 6 (3.8%) Difference: 10.4% (95% CI 5 4.4 to 17.0%) Increased Blood Pressure 1. 7 (4.3%) 2. 1 (0.6%) Difference 3.7% (95% CI 0.4 to 8.1)	10%/ 10 3.7% /27	Patients with moderate to severe lung disease or recent heart disease were excluded. Intervention: Weight-based dosing of 0.3mg/kg and 0.7 mg/kg was evaluated in phase 2 trials. Both doses improved 6MWD compared to placebo in a phase 2 trial, and the higher dose was associated with a numerically improved PVR.[6] Comparator: Placebo appropriate to determine efficacy. All patients were on current standard of care for PAH. Outcomes: 6MWD, WHO functional class improvement, and clinical worsening are relevant clinical outcomes to evaluate exercise capacity, functional ability and worsening PAH symptoms. Clinical worsening is a composite endpoint and the trial was not powered to determine differences in the individual components of the composite. Setting: From January 2021 to August 2022. Enrollment in North America: 32.5%

Abbreviations: 6MWD = 6 minute walking distance; AE = adverse events; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; BMI = body mass index; eGFR = estimated glomerular filtration rate; FVC = forced vital capacity; h/o = history of; HR = hazard ratio; ITT = intention to treat; IV = intravenous; LVEF = left ventricular ejection fraction; m = meters; MD = mean difference; ms = millisecond; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not significant; PAH = pulmonary arterial hypertension; PC = placebo-controlled; PH = pulmonary hypertension; PP = per protocol; PVR = pulmonary vascular resistance; RCT = randomized controlled trial; SC = subcutaneously; ULN = upper limit of normal; WHO = world health organization.

* Clinical worsening defined as listing for lung or heart–lung transplantation, rescue therapy with an approved background treatment or increase in the prostacyclin dose by ≥10%, atrial septostomy, hospitalization [≥24 hours] for PAH, or worsening of PAH defined by both a decline in WHO functional class and a decrease in 6-minute walk distance by ≥15% [confirmed by two tests ≥4 hours but ≤1 week apart]

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Appendix 1: Current Preferred Drug List

Pulmonary Arterial Hypertension Oral and Inhaled Drugs

Generic	Brand	Form	Route	PDL
bosentan	BOSENTAN	TABLET	PO	Y
bosentan	TRACLEER	TABLET	PO	Y
sildenafil citrate	REVATIO	TABLET	PO	Y
sildenafil citrate	SILDENAFIL CITRATE	TABLET	PO	Y
ambrisentan	AMBRISENTAN	TABLET	PO	N
ambrisentan	LETAIRIS	TABLET	PO	N
bosentan	TRACLEER	TAB SUSP	PO	N
iloprost tromethamine	VENTAVIS	AMPUL-NEB	IH	N
macitentan	OPSUMIT	TABLET	PO	N
riociguat	ADEMPAS	TABLET	PO	N
selexipag	UPTRAVI	TAB DS PK	PO	N
selexipag	UPTRAVI	TABLET	PO	N
sildenafil citrate	LIQREV	ORAL SUSP	PO	N
sildenafil citrate	REVATIO	SUSP RECON	PO	N
sildenafil citrate	SILDENAFIL CITRATE	SUSP RECON	PO	N
sildenafil citrate	SILDENAFIL CITRATE	TABLET	PO	N
sildenafil citrate	VIAGRA	TABLET	PO	N
tadalafil	TADLIQ	ORAL SUSP	PO	N
tadalafil	ADCIRCA	TABLET	PO	N
tadalafil	ALYQ	TABLET	PO	N
tadalafil	TADALAFIL	TABLET	PO	N
treprostinil	TYVASO	AMPUL-NEB	IH	N
treprostinil	TYVASO DPI	CART INHAL	IH	N
treprostinil diolamine	ORENITRAM ER	TABLET ER	PO	N
treprostinil diolamine	ORENITRAM MONTH 1 TITRATION KT	TB ER DSPK	PO	N
treprostinil diolamine	ORENITRAM MONTH 2 TITRATION KT	TB ER DSPK	PO	N
treprostinil diolamine	ORENITRAM MONTH 3 TITRATION KT	TB ER DSPK	PO	N
treprostinil/neb accessories	TYVASO REFILL KIT	AMPUL-NEB	IH	N
treprostinil/nebulizer/accesor	TYVASO INSTITUTIONAL START KIT	AMPUL-NEB	IH	N
treprostinil/nebulizer/accesor	TYVASO STARTER KIT	AMPUL-NEB	IH	N

Pulmonary Arterial Hypertension Parenteral Drugs

Generic	Brand	Form	Route	PDL
epoprostenol sodium (glycine)	FLOLAN	VIAL	IV	Y
epoprostenol sodium	EPOPROSTENOL SODIUM	VIAL	IV	N
epoprostenol sodium	VELETRI	VIAL	IV	N
selexipag	UPTRAVI	VIAL	IV	N

sildenafil citrate	REVATIO	VIAL	IV	N
sildenafil citrate	SILDENAFIL CITRATE	VIAL	IV	N
treprostinil sodium	REMODULIN	VIAL	IJ	N
treprostinil sodium	TREPROSTINIL	VIAL	IJ	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to August 29, 2024

1	Bosentan/	1826
2	Sildenafil Citrate/	6011
3	ambrisentan.mp.	521
4	exp Endothelin Receptor Antagonists/	6142
5	Iloprost/	2157
6	macitentan.mp.	480
7	riociguat.mp.	574
8	selexipag.mp.	286
9	Tadalafil/	1784
10	exp Phosphodiesterase 5 Inhibitors/	9480
11	treprostinil.mp.	831
12	Epoprostenol/	12967
13	exp Prostaglandins/	104854
14	sotatercept.mp.	126
15	exp Lung Diseases, Interstitial/	88270
16	exp Hypertension, Pulmonary/	43798
17	guanylate cyclase stimulators.mp.	134
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 17	120518
19	15 or 16	130442
20	18 and 19	5308
21	limit 20 to (english language and humans)	4060
22	limit 21 to yr="2021 -Current"	493
23	limit 22 to (adaptive clinical trial or clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or equivalence trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	138

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use WINREVAIR safely and effectively. See full prescribing information for WINREVAIR.

WINREVAIR™ (sotatercept-csrk) for injection, for subcutaneous use
Initial U.S. Approval: 2024

----------INDICATIONS AND USAGE----------
WINREVAIR is an activin signaling inhibitor indicated for the treatment of adults with pulmonary arterial hypertension (PAH, WHO Group 1) to increase exercise capacity, improve WHO functional class (FC) and reduce the risk of clinical worsening events. (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended starting dose is 0.3 mg/kg by subcutaneous injection. (2.1)
- The recommended target dose is 0.7 mg/kg every 3 weeks by subcutaneous injection. (2.2)
- Dosage modifications due to increased hemoglobin (Hgb) and decreased platelets may be necessary. Check Hgb and platelets before each dose for the first 5 doses, or longer if values are unstable, and monitor periodically thereafter. (2.3)
- See full prescribing information for preparation and administration instructions. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
- For injection: 45 mg lyophilized cake or powder in a single-dose vial (3)
- For injection: 60 mg lyophilized cake or powder in a single-dose vial (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Erythrocytosis: If severe, may increase the risk of thromboembolic events and hyperviscosity syndrome. Monitor Hgb before each dose for the first 5 doses, or longer if values are unstable, and periodically thereafter to determine if dose adjustments are required. (5.1)
- Severe Thrombocytopenia: May increase the risk of bleeding. Monitor platelets before each dose for the first 5 doses, or longer if values are unstable, and periodically thereafter to determine if dose adjustments are required. (5.2)
- Serious Bleeding: Serious bleeding events were reported and were more likely with concomitant prostacyclin and/or antithrombotic agents, or with low platelet counts. Do not administer WINREVAIR if the patient is experiencing serious bleeding. (5.3)
- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.4, 8.1, 8.3)
- Impaired Fertility: May impair female and male fertility. (5.5, 8.3, 13.1)

----------ADVERSE REACTIONS----------
The most common (≥10% in patients receiving WINREVAIR and 5% more than placebo) adverse reactions were headache, epistaxis, rash, telangiectasia, diarrhea, dizziness, and erythema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme LLC at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------USE IN SPECIFIC POPULATIONS----------
Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2024

Appendix 4: Key Inclusion Criteria

Population	People with Pulmonary Arterial Hypertension
Intervention	Drugs in Appendix 1
Comparator	Drugs in Appendix 1
Outcomes	Symptom improvement, exercise capacity, lung function, hospitalizations, mortality
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Pulmonary Hypertension Agents, Oral/Inhaled

Goals:

- Restrict use to appropriate patients with World Health Organization (WHO) Functional Class II-IV symptoms and WHO pulmonary classifications with demonstrated clinical benefit in clinical trials (e.g., pulmonary arterial hypertension (PAH), chronic thromboembolic pulmonary hypertension, or interstitial lung disease).
- Restrict use to conditions funded by the Oregon Health Plan (OHP). Note: erectile dysfunction is not covered by the OHP.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs (pharmacy and provider administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the drug being prescribed by, or in consultation with, a pulmonologist or cardiologist?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
3. Is the request for riociguat (Adempas®) or ambrisentan (Letairis®)?	**Yes:** Go to #4	**No:** Go to #5
4. Is there documentation that the patient has a medical history of PAH associated with idiopathic interstitial pneumonias or idiopathic pulmonary fibrosis?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #5
5. Is the patient classified as having World Health Organization (WHO) Functional Class II-IV symptoms?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is there a diagnosis of pulmonary arterial hypertension (PAH) (WHO Group 1; ICD10 I27.0)?	**Yes:** Go to #7	**No:** Go to #8
7. Will the prescriber consider a change to a preferred product? Note: preferred products do not require PA.	**Yes:** Inform prescriber of preferred alternatives in class.	**No:** Approve for 12 months
8. Is the request for riociguat in a patient with a diagnosis of chronic thromboembolic pulmonary hypertension (WHO Group 4; ICD10 I27.24)?	**Yes:** Approve for 12 months	**No:** Go to #9
9. Is the request for nebulized treprostinil (Tyvaso®) in a patient with WHO Group 3 pulmonary hypertension (ICD10 I27.23) and a diagnosis of interstitial lung disease (J84.0-J84.9)? Note: treprostinil is not approved in patients with pulmonary hypertension due to chronic obstructive pulmonary disease and may increase risk of exacerbations.	**Yes:** Approve for 12 months	**No:** Go to #10
10. Is the request for treatment of erectile dysfunction, sexual dysfunction, or infertility?	**Yes:** Pass to RPh; Deny; not covered by OHP.	**No:** Go to #11

Approval Criteria		
11. RPh Only: For other indications and other types of pulmonary hypertension, prescriber must provide supporting literature for use.	**Yes:** Approve for length of treatment.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *12/24; 10/21 (SS); 9/18; 3/16; 7/14; 3/14; 2/12; 9/10*
Implementation: *1/1/25; 1/1/22; 11/1/18; 10/13/16; 5/1/16; 5/14/12; 1/24/12; 1/1/11*

Pulmonary Arterial Hypertension Agents, Injectable (IV/SC)

Goals:

- Restrict use to patients with pulmonary arterial hypertension (PAH) and World Health Organization (WHO) Functional Class III-IV symptoms.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs (pharmacy and provider administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Will the prescriber consider a change to a preferred product? Note: preferred products do not require PA.	**Yes:** Inform prescriber of preferred alternatives in class.	**No:** Go to #3

Approval Criteria		
3. Is there a diagnosis of pulmonary arterial hypertension (PAH) (WHO Group 1; ICD 10 I27.0)? Note: injectable PAH medications are not FDA-approved for other forms of pulmonary hypertension.	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for a prostanoid or prostacyclin receptor agonist (e.g., treprostinil, epoprostenol, selexipag)?	**Yes:** Go to #5	**No:** Go to #6
5. Is the patient classified as having World Health Organization (WHO) Functional Class III-IV symptoms?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the request for a patient with World Health Organization (WHO) Functional Class II-IV symptoms?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is the drug being prescribed by, or in consultation with, a pulmonologist or a cardiologist?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *12/24 (SS); 10/2; 9/18; 3/16; 9/12*
Implementation: *1/1/25; 10/13/16; 1/1/13*