

KEY FINDINGS

Intervention	Evidence Rating	Annual WAC	Health-Benefit Price Benchmark	Change from Annual Price to Reach Threshold Price
sotatercept (Merck & Co.)	Moderate certainty of a small to substantial net health benefit, with a high certainty of at least a small net health benefit (B+).	Placeholder price: \$400,000	\$17,900 to \$35,400 per year	N/A

“Pulmonary arterial hypertension is a progressive disease that can lead to debilitating shortness of breath, fatigue, and lightheadedness as the heart struggles to pump blood through the lungs. Current drug treatments are primarily combinations of vasodilators, and these can be very burdensome and cause significant side effects. Sotatercept has a novel mechanism of action and it is administered subcutaneously every few weeks, which reduces burdens. Current evidence suggests that sotatercept has fewer side effects and improves short-term outcomes, but we have some uncertainties about long-term efficacy and safety.”

– ICER’s Chief Medical Officer David Rind, MD

THEMES AND RECOMMENDATIONS

- Given sotatercept’s efficacy and safety profile, efforts from all stakeholders are needed to ensure that sotatercept is accessible and affordable to all eligible patients. This includes setting sotatercept’s price in fair alignment with the long-term benefits, rapidly transitioning sotatercept to home-based administration, and ensuring affordability through the combination of benefit design and financial assistance programs.
- For optimal care, access to PAH specialists should be facilitated – particularly across state lines – by ensuring that clinicians are licensed and able to be reimbursed in the appropriate states, COVID-era telemedicine and inter-state consultations remain in effect, and including wraparound coverage for travel to specialists.
- Increasing access to liquid oxygen when medically necessary through reform of supplemental oxygen reimbursement policies, including setting differential reimbursement rates for more expensive forms of oxygen.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Pulmonary arterial hypertension (PAH) is a rare, progressive disease that affects approximately 50,000 to 100,000 people in the US. The disease is characterized by increased pressure in the pulmonary arteries, making it more difficult for the heart to pump blood to the lungs and leading to debilitating symptoms such as shortness of breath, fatigue, chest pain, dizziness, and syncope. PAH can be idiopathic, due to inherited genetic mutations or exposure to drugs or toxins, or associated with congenital heart disease or other systemic diseases such as connective tissue disease, liver disease, or HIV. Quality of life for persons with PAH is generally poor, and depression and anxiety are also common. PAH can substantially shorten lifespan, with one-fifth of patients dying within three years of diagnosis. People with PAH describe a large impact on their lives and the lives of their families both from symptoms and financially, with direct medical costs estimated at more than \$100,000 per person per year.

Current treatment for PAH includes medications that promote vasodilation with the goals of improving functional status and survival. There are several classes of drugs available for treatment: those affecting the nitric oxide pathway, including phosphodiesterase-5 inhibitors (PDE5i, oral with an IV formulation available) and soluble guanylate cyclase stimulators (sGCS, oral); endothelin receptor antagonists (ERA, oral); and prostacyclin analogues (prostanoids; oral, inhaled, subcutaneous (SC), or intravenous (IV) as well as a prostacyclin receptor agonist (oral). Current clinical practice guidelines suggest that low and intermediate risk patients should be initiated on combination therapy with ERA and PDE5i agents; those with high-risk disease should be initiated on triple therapy with the addition of an IV or SC prostacyclin analogue. Ultimately, lung or heart-lung transplantation may be necessary.

Sotatercept (Merck & Co., Inc) is a first-in-class activin signaling inhibitor and potentially disease-modifying drug which may improve pulmonary blood flow through inhibiting cellular proliferation, promoting cellular death, and decreasing inflammation in vessel walls. It is administered as a subcutaneous injection every three weeks. A Biologics License Application for sotatercept has been filed with the US Food and Drug Administration (FDA), with a decision expected by March 26, 2024.

The pivotal trial for sotatercept was STELLAR, a Phase III randomized, placebo-controlled trial of 323 persons with World Health Organization functional class (WHO-FC) II and III PAH. Participants were randomized to receive either sotatercept 0.7 mg/kg every 3 weeks added on to stable background double or triple therapy or continued background therapy. The primary outcome was change in 6-minute walk distance (6MWD) at 24 weeks; WHO-FC, quality of life, hemodynamic, and biomarker outcomes were also measured as secondary endpoints, as well as a multicomponent endpoint combining 6MWD, NT-proBNP level, and WHO-FC change.

Trial participants were mainly female and White, with a mean age of around 48 years and a mean of 8.8 years since diagnosis. Approximately 40% were on infused prostacyclin therapy at baseline. The median difference in 6MWD was 40.8 meters, favoring the sotatercept group. Around twice as many participants in the sotatercept group had improvement in WHO-FC compared with placebo (29.4% vs. 13.8%). There was an 84% reduction in the risk of clinical worsening or death. Secondary outcomes were consistently in favor of sotatercept. Despite patient and provider reports of substantial improvements, overall measurements of quality of life using a PAH-specific scale did not improve with sotatercept although there were

Clinical Analyses

improvements in two of three. Open-label extension trials suggested that improvements in 6MWD, NT-proBNP, and WHO-FC are maintained up to 24 months.

Harms of sotatercept were relatively few, and there were more adverse events, severe adverse events, and discontinuations in the placebo group than in the sotatercept group. There were few deaths overall, but numerically fewer deaths in the sotatercept group. There were additional deaths during open-label extension. The most common adverse events included headache, diarrhea, epistaxis, telangiectasias, and dizziness. Adverse events of concern with sotatercept included a statistically significant higher rate of telangiectasias, increased hemoglobin levels, and bleeding events.

Based on the currently available data, treatment with sotatercept added to background therapy can improve clinical outcomes for patients with PAH, with relatively few harms. Additionally, the subcutaneous delivery system is less burdensome than many other PAH treatments, particularly inhaled and intravenous prostanoids. However, uncertainty remains about sotatercept's efficacy in sicker populations and in those with connective tissue disease, and about the durability of effect. In the absence of longer-term data, we necessarily have uncertainties about sotatercept's effects on mortality and as-yet-undetected adverse effects. Therefore, we have moderate certainty of a small to substantial net health benefit, with a high certainty of at least a small net health benefit, corresponding to an ICER Evidence Rating of B+.

Economic Analyses

LONG-TERM COST EFFECTIVENESS

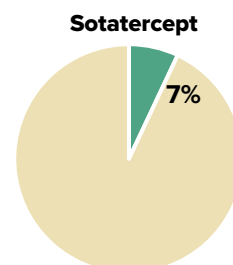
We estimated the cost-effectiveness of sotatercept added to background therapy from a health care sector perspective using a de novo decision analytic model. Treatment with sotatercept resulted in longer time

without symptoms at rest and more quality-adjusted life years (QALYs), life years, and equal value life years (evLYs). The health benefit price benchmark for sotatercept is \$17,900 to \$35,400 per year.

POTENTIAL BUDGET IMPACT

At sotatercept's assumed placeholder price of \$400,000 annually, 7% of the estimated 60,675 eligible patients in the US could be treated within five years without crossing the ICER potential budget impact threshold of \$777 million per year.

In the absence of a known price for sotatercept, ICER is not issuing an access and affordability alert. Stakeholders should be aware, however, that at prices substantially lower than analyst estimates, payers will face a significant short-term budget impact if sotatercept is approved.



Percent of eligible patients with pulmonary arterial hypertension that could be treated in a given year before crossing the ICER potential budget impact threshold

Economic Analyses

The purpose of an ICER access and affordability alert is to signal to stakeholders and policymakers that the amount of added health care costs associated with a new service may be difficult for the health system to absorb over the short term without displacing

other needed services, creating pressure on payers to sharply restrict access, or causing rapid growth in health care insurance costs that would threaten sustainable access to high-value care for all patients.

Public Meeting Deliberations

VOTING RESULTS

ICER assessed, and the independent appraisal committee voted on, the evidence of sotatercept for adults with World Health Organization WHO Functional Class (WHO-FC) II and III pulmonary arterial hypertension (PAH) who are on background therapy:

- All panelists (13-0) found that current evidence is **adequate** to demonstrate a net health benefit for sotatercept when compared to background therapy alone.

Panel members also weighed potential benefits and disadvantages beyond the direct health effects and broader contextual considerations. Voting highlighted the following as particularly important for payers and other policymakers to note:

- The magnitude of the lifetime impact on individual patients with PAH.

About ICER

The Institute for Clinical and Economic Review ([ICER](https://www.icer.org)) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public

hearings through three core programs: the California Technology Assessment Forum ([CTAF](https://www.ctaf.org)), the Midwest Comparative Effectiveness Public Advisory Council ([Midwest CEPAC](https://www.midwestcepac.org)) and the New England Comparative Effectiveness Public Advisory Council ([New England CEPAC](https://www.newenglandcepac.org)). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer.org).