Sotatercept for Pulmonary Arterial Hypertension

Revised Background and Scope

June 13, 2023

Background

Pulmonary arterial hypertension (PAH) is a rare, progressive disease characterized by thickening of the walls of the pulmonary arteries that carry blood from the right side of the heart to the lungs, leading to increased pulmonary vascular resistance. The increased pressure in the pulmonary arteries makes it more difficult for the heart to pump blood to the lungs and leads to debilitating symptoms such as shortness of breath (particularly with exertion), chest pain, fatigue, dizziness, syncope, and leg edema. Eventually, dysfunction of the right ventricle leads to premature death, with one-fifth of patients dying within 3 years of diagnosis.[1] The impact of PAH is significant, with direct medical costs estimated at $100,000 per person per year.[2]

Fewer than 50,000 persons in the United States (US) have PAH, which is estimated to occur in 15 to 50 persons per million in the population.[1] The disease is more common in women than men, with onset generally between the ages of 30-60 years. Although the majority of persons with PAH are White, there are racial and ethnic differences in presentation. For example, Black persons with PAH were more likely to be younger, female, and have an associated connective tissue disorder.[3] PAH can be idiopathic, due to inherited genetic mutations or exposure to drugs or toxins (e.g., fenfluramine, methamphetamines), or associated with other conditions such as connective tissue disease, congenital heart disease, HIV, portal hypertension, and schistosomiasis. Since the symptoms can be mild and nonspecific at first and the diagnosis of PAH requires exclusion of other causes of pulmonary hypertension[4], diagnosis is often delayed by more than 2 years.[5]

Treatment for PAH includes supportive care such as exercise training, oxygen supplementation, iron supplementation, referral for drug rehabilitation as needed[6], and treatment of anxiety and depression[7]. It often also involves pharmacologic therapy with goals of improving functional status and survival.[8] Currently available pharmacologic agents for PAH treatment promote vasodilation and include oral phosphodiesterase 5 inhibitors (PDE5i), oral endothelin receptor antagonists (ERA), oral soluble guanylate cyclase stimulators (sGCS), and prostacyclin and prostacyclin receptor analogues (oral, inhaled, subcutaneous, or intravenous). Intensity of therapy is based on whether a person has a low, intermediate, or high risk of death as calculated through various prognostic indicators such as World Health Organization Functional Class (WHO-FC), 6-minute walk distance

(6MWD), and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels.[9] Current clinical practice guidelines suggest that low and intermediate risk patients should be initiated on combination therapy with ERA and PDE5i agents; the addition of other agents such as selexipag may be considered in some cases.[8] Those with high-risk disease are recommended to be initiated on triple therapy with the addition of an intravenous or subcutaneous prostacyclin analogue to combination therapy.[8] Ultimately, lung or heart-lung transplantation may be necessary. Treatment of PAH has been shown to improve pulmonary hemodynamics, exercise capacity and progression-free survival; however, even with treatment, median survival after diagnosis is 5 to 7 years.[10]

Sotatercept (Merck & Co., Inc) is a first-in-class activin signaling inhibitor which may improve pulmonary blood flow through inhibiting cellular proliferation, promoting cellular death, and decreasing inflammation in vessel walls.[11] Unlike current therapies, which work mainly via vasodilation, sotatercept's mechanism of action is distinct and is felt by some to potentially disease-modifying. It has been studied as a subcutaneous injection every 3 weeks added on to stable background therapy. A Biologics License Application is expected to be filed with the US Food and Drug Administration in 2023.

Stakeholder Input

The draft scoping document was developed with input from diverse stakeholders, including patients and their families, clinicians, researchers, and manufacturers of the agents of focus in this review. This revised scoping document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. Based on the feedback received, we clarified the comparator and further describe the experience of people living with PAH. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of treatments for PAH.

PAH has substantial impacts on quality of life, including physical, emotional, social, and financial burdens. The symptoms of PAH can be pervasive, including constant shortness of breath and fatigue, which can limit participation in activities or make them much harder to do. For example, people with PAH describe difficulty doing daily living tasks such as laundry, washing dishes, and cooking, and also having to stop participating in activities that they had once enjoyed due to their symptoms. Symptoms can also lead to substantial life changes including the need to leave the workforce, moving to a lower elevation, and altering family planning.

Because symptoms can initially be generalized and nonspecific, there is often a delay both in seeking medical attention and in diagnosis, which can impact both survival and quality of life. Once a diagnosis is made, people with PAH describe currently available therapies as burdensome to manage in terms of administration, side effects, and financially. For example, oral and inhaled medications may need to be taken several times per day and intravenous medications require continuous infusions through a catheter. In addition to the burdens of having to have medication

being infused 24 hours a day, having a catheter involves the need for meticulous handling to avoid catheter-associated infections.

People with PAH also mentioned that currently available treatments often have substantial side effects, including nausea, vomiting, diarrhea, flushing, and dizziness, which can limit their use. Additionally, access to prescription drugs can be difficult, as they can be expensive, subject to prior authorization, and available only through specialty pharmacies; getting timely refills and deliveries can be challenging. Finally, people with PAH expressed hope that future treatments would have less complex regimens and less burdensome administration to allow for more freedom and flexibility in their lives, and were excited by the results of the sotatercept clinical trials.

Report Aim

This project will evaluate the health and economic outcomes of sotatercept for PAH. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population for the review is adult patients with Pulmonary Arterial Hypertension WHO Functional Class II/III who are on stable background therapy, defined as therapy with agents from the following classes:

- endothelin receptor antagonists (ERA)

- phosphodiesterase 5 Inhibitors (PDE5i)

- soluble guanylate cyclase stimulators (sGC)

- prostacyclin receptor agonist

- prostacyclin analogues (prostanoids)

Data permitting, we will evaluate the evidence for subpopulations defined by:

- Age

- Sex (male, female)

- Race and Ethnicity (White, Black, Hispanic, Asian, other)

- PAH Diagnostic group (idiopathic, heritable, drug/toxin-induced, connective tissue disease, congenital heart disease with systemic to pulmonary shunt repair)

- Baseline background therapy

    o Double therapy

    o Triple therapy

- Baseline WHO Functional Class (II, III)

- Baseline pulmonary vascular resistance

Interventions

Our intervention of interest for this review is sotatercept (Merck & Co, Inc.) added to standard of care.

Comparators

Data permitting, we intend to compare sotatercept added to standard of care to standard of care alone as estimated by the placebo arm in clinical trials. We recognize that in some patients, PAH treatment can include a third oral therapy such as an oral prostacyclin or prostacyclin receptor agonist before an infused or injectable prostacyclin is prescribed. However, based on input from clinical experts and our review of market analysis databases, these medications are variably used and thus we will not consider them to be separate comparators to sotatercept.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Mortality
    - Improvements in exercise capacity (e.g., 6 Minute Walk Distance)
    - Health related quality of life (e.g., PAH-Symptoms and Impact questionnaire)
    - Risk of clinical worsening (e.g., French score, WHO Functional Class, hospitalizations, Registry to Evaluate Early and Long-Term PAH Disease Management [REVEAL] Risk Score)
    - Ability to maintain employment
    - Need for lung or heart-lung transplant
    - Need for additional symptomatic agents
    - Adverse events including
        - Treatment-related mortality
        - Serious adverse events
        - Treatment-related discontinuation
- Other Outcomes
    - Changes in cardiac related biomarkers (e.g., NT-proBNP levels)
    - Changes in hemodynamic endpoints (e.g., pulmonary vascular resistance, mean pulmonary artery pressure)

Timing

Evidence on intervention effectiveness and harms will be derived from studies of at least three months duration.

Settings

All relevant settings will be considered, including both inpatient and outpatient.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.2. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages

Contextual Consideration*
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability
Magnitude of the lifetime impact on individual patients of the condition being treated
Other (as relevant)

*Contextual considerations refer to social or ethical priorities that shape to some extent how the value of any effective treatments for a particular condition will be judged.

Potential Other Benefit or Disadvantage*
Patients' ability to achieve major life goals related to education, work, or family life
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life
Patients' ability to manage and sustain treatment given the complexity of regimen
Society's goal of reducing health inequities
Other (as relevant)

*Potential other benefits or disadvantages are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of sotatercept added on to standard care as compared to standard care alone. The model structure will be based in part on a literature review of prior published models of PAH.[12-14] The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. The starting population will consist of adults with PAH in WHO Functional Class II or III who are on standard of care therapy, i.e. double or triple background therapy. The model will consist of health states defined by WHO functional class, transplant, and death and will include separate health states for Functional Class I, Functional Class II, Functional Class III, Functional Class IV, Post-Transplant, and Death. A cohort of patients will transition between states during predetermined cycles of 12 weeks over a lifetime time horizon, modeling patients from treatment initiation until death.

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated from best available evidence including the pivotal randomized controlled trial, and may include differences in functional class, mortality, health system utilization, and standard care pharmaceutical utilization as data suggest.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcomes of each intervention will be evaluated in terms of time spent without symptoms at rest (defined as time spent in WHO Functional Classes I-III), life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLYG). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, productivity changes and other indirect costs will be included in a separate analysis if available data allow. Results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life-year gained, and cost per additional year without symptoms at rest.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model

for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by sotatercept (e.g., reduced need for hospitalizations), as such services will be captured in the economic model. Rather, we are seeking services used in the current management of PAH beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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