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Reimbursement Recommendation

Sotatercept (Winrevair)

Indication: In combination with standard pulmonary arterial hypertension (PAH) therapy, for the treatment of adults with World Health Organization Group 1 PAH and Functional Class II or III.

Sponsor: Merck Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Canada's Drug Agency Reimbursement Recommendation for Winrevair?

Canada's Drug Agency (CDA-AMC) recommends that sotatercept (Winrevair) should be reimbursed by public drug plans for the treatment of patients with WHO Group 1 pulmonary arterial hypertension (PAH) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Winrevair should only be covered as add-on therapy in patients with confirmed WHO Group 1 PAH based on guidelines-approved diagnostic procedure including right-heart catheterization (RHC).

What Are the Conditions for Reimbursement?

Winrevair should only be reimbursed as an add-on therapy in patients who are not at low risk, currently treated with optimal background therapy for at least 3 months, and if the cost of Winrevair is reduced.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 1 randomized trial demonstrated that in patients with symptomatic PAH in WHO functional class (FC) II or III who were receiving stable doses of background PAH therapy for at least 3 months before enrolment, Winrevair, when added to optimal background therapy, significantly improved clinical outcomes, such as the 6-minute walk distance (6MWD), WHO FC, improved health-related quality of life (HRQoL), and reduced PAH-specific hospitalizations, compared to placebo.
- Based on our assessment of the health economic evidence, Winrevair does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Winrevair is estimated to cost public drug plans approximately $285 million over the next 3 years.

Additional Information

What Is PAH?

PAH is a serious condition where the blood pressure in the arteries of the lungs is abnormally high, making it harder for the heart to pump blood through the lungs and leading to symptoms like shortness of breath, fatigue, and heart strain. It is a rare disease affecting approximately 7 to 8 people per 100,000 of the population in Canada. The life expectancy of patients with PAH decreases sharply over time, with the 1-, 3-, and

Summary

5-year survival rates in Canada reported to be 89.2%, 75.6%, and 56.0%, respectively.

Unmet Needs in PAH

Patients with PAH need access to treatments with an acceptable safety profile that slow disease progression and improve exercise capacity, functional status, and HRQoL.

How Much Does Winrevair Cost?

Treatment with Winrevair is expected to cost approximately $199,249 per patient per year in the first year, and $202,155 per patient per year in subsequent years, assuming a patient weight of 70 kg.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that sotatercept be reimbursed in combination with standard PAH therapy, for the treatment of adults with WHO Group 1 PAH and FC II or III only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from a double-blind placebo-controlled (DBPC) phase III randomized trial (STELLAR; N = 323 patients) demonstrated that sotatercept, when added to optimal background therapy, provides significant clinical benefits in patients with symptomatic PAH in WHO FC II or III who were receiving stable doses of background PAH therapy for at least 3 months before enrolment. Specifically, compared with placebo, patients treated with sotatercept showed more significant improvement from baseline in the 6MWD at week 24, with a between-group difference of 40.8 m (95% CI, 27.5 to 54.1). More patients treated with sotatercept met all 3 composite end-point criteria (6MWD, N-terminal pro–B-type natriuretic peptide [NT-proBNP] levels, and WHO FC), with a between-group difference of [redacted]), compared with patients treated with placebo. CDEC noted that a Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment indicated high-certainty evidence regarding the clinical effectiveness of sotatercept based on these outcomes.

CDEC acknowledged clinicians' and patients' identified unmet needs, such as treatments that slow disease progression and improve function and HRQoL. CDEC noted that a GRADE assessment of the results from the STELLAR trial indicated a high certainty that compared with placebo, add-on treatment with sotatercept likely improves patients' WHO FC and reduces PAH-specific hospitalizations, with a moderate certainty of improving HRQoL. Therefore, CDEC concluded that sotatercept met some of the unmet needs identified by patients and clinicians.

Using the sponsor-submitted price for sotatercept and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for sotatercept in addition to optimal background therapy was $436,796 per quality-adjusted life-year (QALY) gained compared with optimal background therapy alone for adult patients with PAH who are not at low risk. The results are driven by the drug acquisition cost, and estimated extension in life and treatment usage (4.3 years). The drug acquisition cost of sotatercept is $199,249 per patient in the first year and $202,155 per patient in subsequent years (based on a weight of 67.5 kg to 88.9 kg), resulting in a lifetime sotatercept drug acquisition cost of $1,561,624 per patient. As such, price reductions to current optimal background treatment in addition to sotatercept are required for sotatercept to provide optimal value to the public drug plans when added to optimal background treatment.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Sotatercept should be reimbursed only in patients with confirmed WHO Group 1 PAH based on guidelines-approved diagnostic procedure including right heart catheterization.	The inclusion criteria of the STELLAR trial required patients had a confirmatory diagnostic procedure that included right heart catheterization. The clinical experts consulted for the review confirmed that the requirement aligns with clinical practice in Canada. Evidence from the STELLAR trial showed that treatment with sotatercept resulted in benefits to patients with these characteristics.	—
2. Sotatercept must only be reimbursed as add-on therapy in patients who are currently treated with an optimal background therapy for PAH of at least 3 months.	The inclusion criteria in the STELLAR trial states that patients must be receiving stable doses of background therapy for at least 90 days before screening. The breakdown of patients who had monotherapy, dual therapy, or triple therapy as background in the trial was 4.0%, 34.4%, and 61.6%, respectively. Clinical experts believed background therapy duration should be between 3 to 6 months.	According to the clinical experts consulted for this review, add-on sotatercept may be considered after 3 to 6 months of optimal therapy. Optimal background therapy is defined as patients receiving optimal number and doses of therapies according to clinical guidelines. The definition should rely on the latest clinical guidelines developed by organizations of experts in the field of PAH. Clinical variations may exist when defining optimal therapy and should be addressed by treating physicians on a case-by-case basis. For instance, patients may be receiving double or triple therapy depending on individual contraindications and/or tolerability of available PAH therapies. Current drug classes used as background therapy in Canada include ERAs, PDE5i, and prostacyclin analogues or prostacyclin receptor agonists.
3. Sotatercept must be used in patients who are not at low risk.	In the STELLAR trial, 83.4% of patients included were categorized as not low risk.	Low risk is defined by COMPERA 2.0 or Simplified French Risk Score as: • FC I or II and • 6MWD > 440 m • NT-proBNP < 300 ng/L or BNP < 100 ng/L.
Renewal		
4. Assessment for clinical response should occur every 12 months.	Annual assessments will help ensure the treatment is used for those benefiting from the therapy and would reduce the risk of unnecessary treatment.	—

Reimbursement condition	Reason	Implementation guidance
5. For renewal after initial authorization, clinicians must provide proof of beneficial clinical effect, defined as stability or improvement in the patient's risk status when requesting continuation of reimbursement.	In the STELLAR trial, 95% of patients treated with sotatercept remained stable or improved in their functional status.	CDEC noted that beneficial clinical effects should be attested by the attending clinician based on professional judgment.
Discontinuation		
6. Patient has undergone lung transplant.	The clinical experts consulted for the review recommended that the treatment should be discontinued in patients who receive a lung and/or heart transplant.	Patients who are on the list for lung and/or heart transplants can continue being reimbursed until the procedure takes place, based on the professional judgment of the attending physician.
Prescribing		
7. Sotatercept should be prescribed by clinicians with expertise in managing PAH.	This is to ensure that sotatercept is prescribed for appropriate patients and that monitoring is optimized and timely.	—
Pricing		
8. A reduction in price.	The ICER for sotatercept plus optimal background therapy is $436,796 per QALY gained when compared with optimal background therapy alone. A significant price reduction for sotatercept (> 90%), in addition to a 50% price reduction from public list prices for all drugs comprising optimal background therapy, would be required for sotatercept to provide optimal value to the health system.	—
Feasibility of adoption		
9. The economic feasibility of adoption of sotatercept must be addressed.	At the submitted price, the incremental budget impact of sotatercept is expected to be greater than $40 million in years 1, 2, and 3.	—

6MWD = six-minute walking distance test; B-type natriuretic peptide; CDEC = Canadian Drug Expert Committee; ERA = endothelial receptor antagonists; FC = functional class; ICER = incremental cost-effectiveness ratio; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PAH = pulmonary arterial hypertension; PDE5i = phosphodiesterase type 5 inhibitor; QALY = quality-adjusted life-year.

Discussion Points

- The committee noted that patients in the STELLAR trial were receiving stable doses of background PAH therapy for at least 3 months, and the reimbursement request aligns with the Health Canada–approved indication for sotatercept as an add-on to optimal background therapy. CDEC acknowledged the clinical experts' explanation that optimal background therapy may vary based on patient and other clinical factors. Current drug classes used as background therapy in Canada

include endothelial receptor antagonists (ERAs), phosphodiesterase type 5 inhibitors (PDE5i), and prostacyclin analogues or prostacyclin receptor agonists.

- CDEC also discussed the optimal positioning of sotatercept as an add-on therapy for patients with PAH who are not low risk. The committee noted that sotatercept would be an option in patients who have an absolute contraindication to or who have not tolerated treatment with the components of triple therapy combination or cannot tolerate other drug classes while on a single or dual therapy, or those not meeting treatment targets on dual therapy as an alternative to selexipag when considering escalating to triple therapy.
- CDEC noted the current lack of data to guide the renewal, switching, or discontinuation of the drug based on clinical response. The committee acknowledged the clinical experts' explanation that response to treatment is assessed using multiple factors such as FC improvements, 6MWD test results, right ventricular function, hemodynamic measurements, overall quality of life, disease stabilization, or a slowed disease progression rate. CDEC decided that renewal after initial authorization should be based on beneficial clinical effects attested by the attending clinician based on professional judgment.
- CDEC noted that although the sponsor's long-term study was intended to have a 72-week duration, the follow-up was 45 weeks and 39 weeks in the sotatercept and placebo groups, respectively. The committee decided that the considerably shorter follow-up duration and attritional losses make it challenging to draw a definite conclusion on the long-term benefits of sotatercept.
- The committee discussed the economic evidence for sotatercept and noted that sotatercept plus optimal background therapy was associated with 4.09 incremental QALYs and 4.31 additional life-years at an additional cost of $1,786,879. The incremental cost is driven by direct treatment costs (sotatercept and optimal background therapy), which make up 96% of the total costs associated with treatment with sotatercept plus optimal background therapy. The committee noted that, based on both the sponsor's analysis and our analysis, there was no price reduction that would allow sotatercept to achieve an ICER of $50,000 per QALY gained. If the prices for all treatments included in optimal background therapy were 50% lower than their public list prices, a price reduction for sotatercept of approximately 95% would be necessary for it to be considered cost-effective at a threshold of $50,000 per QALY gained (reflecting an annual drug cost of $7,970 and $8,086, in the first and subsequent years of treatment with sotatercept). The committee noted the uncertainty associated with the underlying clinical evidence, specifically duration of treatment effect and the use of surrogate outcomes to inform final outcomes, which may result in a higher ICER than we estimated.

Background

PAH, classified as WHO group 1 pulmonary hypertension, is a rare, highly progressive, and disabling chronic disease. It is characterized by the uncontrolled proliferation of endothelial and smooth muscle cells in the pulmonary arteries, leading to vascular remodelling, increased pulmonary arterial pressure, and right heart dysfunction. This results in progressive symptoms like dyspnea, fatigue, dizziness, and chest pain,

ultimately leading to right heart failure and reduced quality of life and survival. The disease has a complex pathophysiology involving the transforming growth factor-beta superfamily and is more prevalent in females, with a median diagnosis age of 62.5 years. Despite advances in treatment, PAH has a poor prognosis, with a 5-year survival rate of about 56% in Canada. The prevalence of PAH in Canada is estimated at 78 per 1,000,000 population, based on registry data, with considerable variation in global estimates due to different study methodologies.

PAH has nonspecific signs and symptoms. The diagnostic process includes cardiac biomarkers like B-type natriuretic peptide (BNP) and NT-proBNP. Echocardiograms can reveal abnormalities in the right ventricular chamber and interventricular septum. The gold standard for diagnosing PAH is RHC, an invasive procedure that directly measures pulmonary artery pressure and flow. The current definition of PAH, based on RHC, is a mean pulmonary arterial pressure of more than 20 mm Hg, pulmonary arterial wedge pressure of 15 mm Hg or less, and a pulmonary vascular resistance (PVR) of more than 2.0 wood units. Risk status in PAH can be assessed using methods like COMPERA 2.0 or the Simplified French Risk Score. Both methods evaluate 3 noninvasive parameters: WHO FC, 6MWD, and BNP or NT-proBNP levels, using the same cut-off values. The COMPERA 2.0 risk assessment assigns grades 1 through 4 to each parameter and calculates the risk status based on the average score. In contrast, the Simplified French Risk Score requires meeting all low-risk criteria to achieve a low-risk status. These parameters are clinically relevant and correlate with long-term survival in patients with PAH.

Sotatercept received a Health Canada Notice of Compliance on August 28, 2024. Sotatercept is an activin signalling inhibitor for activin-A and it is available as subcutaneous injection at a recommended dose of 0.3 mg/kg, with a targeted dose of 0.7 mg/kg administered every 3 weeks.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 pivotal study (randomized controlled trial [RCT]) in adults with PAH and 3 long-term extension studies
- patients' perspectives gathered by 1 patient group: the Pulmonary Hypertension Association (PHA) of Canada (PHA Canada)
- input from public drug plans that participate in the CDA-AMC review process
- 3 clinical specialists with expertise diagnosing and treating patients with PAH
- input from 1 clinician group: the Canadian Pulmonary Hypertension Health-Care Providers
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to our call for input and from clinical expert(s) we consulted for the purpose of this review.

Patient Input

CDA-AMC received a submission from PHA Canada, which included patient and caregiver survey data and insights. PHA Canada, a charity focused on supporting the pulmonary hypertension community, collaborated with several organizations to gather information on patients' experiences and expectations for sotatercept. The survey found that most respondents were adults with PAH, with idiopathic PAH and scleroderma-associated PAH being the most common subtypes. Diagnosing PAH often takes over 2 years due to its nonspecific symptoms, leading to advanced disease at diagnosis. The disease significantly impacts patients' daily lives and work productivity, with many experiencing severe limitations in physical activities and requiring caregiver assistance.

The socioeconomic burden of PAH is considerable, with many patients underemployed or dependent on assistance. The survey highlighted that current therapies are only somewhat effective in managing symptoms, particularly the psychological and emotional impacts. Adverse effects of medications are common, and patients face barriers to accessing treatments. Patients and caregivers expressed a willingness to tolerate serious adverse effects for benefits such as slowed disease progression, improved quality of life, and better symptom management. Only a few patients reported their experience using sotatercept, likely through clinical trials, and 1 patient from the US shared positive outcomes from the drug's use.

Clinician Input

Input From Clinical Experts Consulted by CDA-AMC

The following input was provided by 3 clinical specialists with expertise in the diagnosis and management of PAH.

Clinical experts highlighted significant unmet needs in treating PAH due to its rarity and lack of curative treatments. Key issues included the heterogeneous drug response among patients, limited options for right heart failure, and scarce guidelines for mixed phenotype PAH or PAH with comorbidities. Additionally, the experts mentioned that there is insufficient data on when to switch or stop treatments based on patient response, and treatment side effects hinder adherence and tolerance.

In terms of the place in therapy, sotatercept, targeting a novel pathway in PAH biology, may show promise in improving outcomes when added to existing therapies, especially for patients whose disease is not well-controlled. The experts mentioned that in the face of scarce evidence, sotatercept should be used as an addition to established treatments rather than a first-line therapy. The novel mechanism could significantly impact patients not meeting treatment goals with current therapies and offer an alternative to chronic infusions. The experts suggested that for new patients with PAH who are not high risk, dual therapy with PDE5 inhibitors and ERAs remains the initial recommendation before considering sotatercept.

Ideal candidates for sotatercept are patients with PAH, especially those in WHO Group 1 pulmonary hypertension on 2 to 3 background therapies without achieving treatment goals. It may also be considered for patients on single therapy if they cannot tolerate other drugs. Patient selection should involve thorough evaluation by specialists who treat PAH, including RHC, and consideration for those not reaching low-risk status after standard therapies. Treatment efficacy should be assessed with 6MWD, BNP or NT-proBNP levels, and clinical assessments. Assessing the response to treatment should be through FC improvements, 6MWD results, right ventricular function, hemodynamic measurements, and overall quality of life. The clinical experts also considered disease stabilization or a slowed disease progression rate as a meaningful response. Initial treatment response is typically evaluated within 4 weeks, with a full assessment at 3 months. If deterioration occurs, earlier reassessment and treatment adjustment may be necessary.

According to the experts, discontinuation of treatment should be considered for patients experiencing significant adverse events (AEs), like bleeding or telangiectasias, if these significantly impact their quality of life. The decision to discontinue, especially in cases of telangiectasias, should be made on a case-by-case basis, weighing the benefits of continued therapy against the side effects. Treatment should also be stopped if the patient has had a lung transplant.

The clinical experts emphasized that sotatercept should be managed within specialized PAH centres staffed by trained cardiologists or respirologists. These specialists are essential for diagnosing, treating, and monitoring patients with PAH, ensuring comprehensive and high-quality care.

Clinician Group Input

The Canadian Pulmonary Hypertension Health-Care Providers, a non-affiliated group of physicians and nurse practitioners from specialized pulmonary hypertension centres, provided input on the current state and challenges in PAH treatment. Their insights are based on the 2022 European Society of Cardiology-European Respiratory Society guidelines, the 2020 Canadian Cardiovascular Society-Canadian Thoracic Society position statement, recent multicentre PAH studies in Canada, and their collective clinical experience. They emphasized that while current treatment options, ranging from nonpharmacologic management to combination therapy and lung transplant, offer symptomatic benefits and stability, these are often short-lived. Current PAH medications act mainly as vasodilators and have minimal impact on blocked vessels or the underlying cellular proliferation, leading to disease progression. Despite optimal medical therapy, few patients achieve low-risk status, with a 5-year survival rate of only about 60% in Canada. Key end points for patients in Canada include improving symptoms, quality of life, survival, and reducing clinical deterioration.

The clinician group highlighted significant unmet needs in PAH treatment, such as the inability of current therapies to halt or reverse cell proliferation and vessel remodelling. They also noted the intolerable side effects and complications associated with parenteral therapies. They view sotatercept, the first approved PAH therapy targeting growth factor signalling to control aberrant cell proliferation, as a promising add-on therapy rather than a first-line treatment. Sotatercept is expected to benefit patients across common PAH types and major FCs II and III. The clinician group emphasized the importance of early aggressive treatment

in PAH. The group recommends that prescribing sotatercept be restricted to provincially designated pulmonary hypertension (PH) centres.

Drug Program Input

The drug programs provide input on each drug being reviewed through CDA-AMC Reimbursement Review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts we consulted are summarized in Table 2.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The sponsor proposes that there are no comparators for sotatercept and notes that all currently available PAH-specific medications in Canada are vasodilators (e.g., phosphodiesterase type 5 inhibitors, endothelin receptor antagonists, prostanoids), whereas sotatercept is a novel activin signalling inhibitor that "may reverse the characteristic pulmonary vascular remodelling in PAH." **Comments** • It is unclear how many plans currently permit triple therapy for patients with PAH and the proposed reimbursement criteria position for sotatercept as part of a triple or quadruple therapy regimen. • It is also unclear how many plans have clearly defined objective renewal criteria for current PAH therapies.	This is a comment from the drug programs to inform CDEC deliberations.
Considerations for initiation of therapy	
The sponsor notes that a confirmative diagnosis of PAH requires an invasive RHC performed by specialists within the PH COEs located across Canada.	This is a comment from the drug programs to inform CDEC deliberations.
Patients in the pivotal trial were required to be receiving stable doses of their respective background PAH therapy for at least 3 months before enrolment and the sponsor is requesting reimbursement as add-on to optimal background therapy. **Comment or question** • If recommended for funding, it will be important to clearly define optimal background therapy.	Clinical experts described that optimal background therapy is well known and defined among experts in PAH and based in current clinical guidelines. They acknowledged that the optimal number and combination of drugs is used according to the patients' risk status and with the goal to achieve or maintain a low-risk status. Clinical experts emphasized that although optimal background therapy is defined by guideline recommendations, patient tolerance is important, and with the significant side effect profile of some of these drugs, maximally tolerated optimal medical therapy" can be different than "optimal background therapy.
Considerations for continuation or renewal of therapy	
The sponsor notes that: • Noninvasive assessments to determine risk status are used for treatment decision-making.	Clinical experts acknowledged that achieving or maintaining low-risk status is 1 of the main goals of treatment and considered that maintaining or improving the patients' risk status would be enough for continuing therapy.

Implementation issues	Response
• The foundation of modern risk assessment includes exercise capacity, 6MWD test, WHO FC, and cardiac biomarkers (e.g., NT-proBNP). • Achieving or maintaining a low-risk status is the goal of treatment and is predictive of significantly better long-term survival. **Question** Should there be a minimum response to therapy to justify continuation of the intervention? If so, how should it be defined, both at the first renewal assessment and afterwards?	The experts recognized that there are no targeted markers to define if and how a patient is responding, and if observing deterioration (an increase) in the patient risk status would suggest considering a discontinuation or to try to escalate therapy. The experts acknowledged that the evidence to establish the best continuation or discontinuation criteria is unclear.
Considerations for prescribing of therapy	
Comment • It is recommended that hemoglobin and platelet count be reviewed before each dose until stable, and then periodically to determine if dose adjustments are required • As noted by the sponsor, sotatercept should be prescribed under the direction of a specialist in PAH.	This is a comment from the drug programs to inform CDEC deliberations.
Generalizability	
Those with a diagnosis of the PAH associated with HIV, portal hypertension, schistosomiasis, and pulmonary veno-occlusive disease were excluded from the pivotal trial. **Question** Should the abovementioned patients be excluded from treatment eligibility?	Clinical experts considered that patients with these conditions should not be excluded from the outset for treatment with sotatercept and rather be considered on a case-by-case analysis to achieve individualized decisions.
System and economic issues	
Comment Comparing to background therapy alone, the BIA predicts that funding of sotatercept in adults with PAH who are not at low risk on optimal background therapy would result in incremental total costs of $38,782,232 in year 1, $82,425,708 in year 2, and $115,650,464 in year 3, for a total incremental cost of $236,858,404 over the 3-year projection period.	This is a comment from the drug programs to inform CDEC deliberations.

6MWD = 6-minute walk distance; BIA = budget impact analysis; CDEC = CDA-AMC Canadian Drug Expert Committee; COE = Centres of Excellence; FC = functional class; NT-proBNP = N-terminal pro–B-type natriuretic peptide levels; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; RHC = right heart catheterization.

Clinical Evidence

Systematic Review

Description of Studies

The systematic review included 1 pivotal study. The STELLAR trial (NCT04576988), a phase III, randomized, multicentre, DBPC study, evaluated the efficacy and safety of sotatercept versus placebo on stable background PAH therapy in adults with WHO Group 1 PAH. The trial was conducted across 21 countries,

including 3 sites in Canada, from January 2021 to December 2022, and enrolled 323 participants with age and gender distributions reflecting typical PAH demographics. The study had 2 treatment periods: a 24-week DBPC phase and a long-term double-blind (LTDB) phase lasting up to 72 weeks or until unblinding. Participants completing the DBPC phase could join a long-term follow-up study, SOTERIA (NCT04796337). Participants were randomized 1:1 to receive sotatercept or placebo subcutaneously every 21 days, starting at 0.3 mg/kg and increasing to 0.7 mg/kg, with adjustments as needed. The trial included 163 participants in the sotatercept group and 160 in the placebo group, with analyses conducted on the full analysis set and safety set.

Overall, patients had a mean age of 47.9 years. Almost one-half were in WHO FC III (166 of 323 randomized [51.4%]) with equal distribution between placebo and sotatercept groups. Other patients were classified as WHO FC II. The mean time from diagnosis was 8.8 years for all patients. The study shows no significant differences in the baseline characteristics between study arms.

Efficacy Results

Mortality

In the STELLAR trial, mortality, (i.e., the number of patients who died during the follow-up of the study), was assessed as part of a multicomponent end point (also described in the following) at the final cut-off date of December 6, 2022. Overall, the number of patients who died were relatively low — less than 4%. More deaths were observed in the placebo arm (6 patients died [3.8%]) than in the sotatercept arm (2 patients died [1.2%])

Change From Baseline in 6MWD

Sotatercept significantly improved the 6MWD in adults with PAH receiving background therapy, with a median treatment difference between the sotatercept and placebo groups of 40.8 m (95% CI, 27.5 to 54.1) at 24 weeks. The improvement was greater in patients within the WHO FC III stratum (61.7 m; 95% CI, 40.9 to 82.6) than in those in the WHO FC II stratum (21.7 m; 95% CI, 6.6 to 36.7)

Multicomponent Improvement

At week 24, a higher proportion of patients in the sotatercept group (38.9%) met all criteria for improvement in the multicomponent end point (6MWD, NT-proBNP level, and WHO FC) compared to the placebo group (10.1%). The risk difference between groups was [redacted].

Time to Clinical Worsening or Death

By the December 2022 data cut-off, fewer participants in the sotatercept group (11 [6.7%]) than in the placebo group (42 [26.3%]) died or had at least 1 clinical worsening event. The risk difference between groups was [redacted]), this is, a reduction in the risk of the composite end point in favour of sotatercept. Evaluating this composite end point as time to event outcome, the risk of death or a first clinical worsening event was 82% lower in the sotatercept group compared with the placebo group (hazard ratio = 0.18; 95% CI, 0.09 to 0.38).

When evaluating the individual components of the composite end point, more patients in the placebo arm (17 patients [10.6%]) required rescue therapy or an increase in the dose of infusion prostacyclin than in the sotatercept arm (2 patients [1.2%]). PAH-related hospitalization was observed in 7 patients in the placebo arm and 1 in the sotatercept arm (4.4% versus 0.6%). As mentioned in the mortality outcome section, 2 patients in the sotatercept arm died compared to 6 from the placebo arm.

Change From Baseline in PVR

Patients in the sotatercept arm demonstrated a reduction in pulmonary artery resistance (PVR) from baseline to week 24 of −165.1 dyn·sec·cm^{-5} (95% CI, −184.0 to −152.0), whereas the PVR increased in the placebo arm by 32.8 dyn·sec·cm^{-5} (95% CI, 24.0 to 40.0). The median treatment difference between the sotatercept and placebo groups was −234.6 dyn·sec·cm^{-5} (95% CI, −288.4 to −180.8). Results from the supportive analysis using the analysis of covariance (ANCOVA) model were consistent with those from the primary analysis. The treatment effect of sotatercept on PVR at week 24 was consistent across the prespecified subgroups and remained consistent in the post hoc subgroups stratified by baseline risk status.

Change From Baseline in NT-proBNP

The median treatment difference between the sotatercept and placebo groups in mean change from baseline was −441.6 pg/mL (95% CI, −573.5 to −309.6). Results from the supportive analysis using the ANCOVA model were consistent with those from the primary analysis. The treatment effect of sotatercept on NT-proBNP at week 24 was consistent across the prespecified subgroups and remained consistent in the post hoc subgroups stratified by baseline risk status.

WHO FC Improvement

More patients in the sotatercept group (29.4%) showed improvement in WHO FC at week 24 compared to the placebo group (13.8%). The risk difference was [redacted]. Specifically, more patients in the sotatercept group than placebo group improved from WHO FC II to FC I (5.0% versus 2.0%, respectively), and from WHO FC III to FC II (24.5% versus 12.2%, respectively) at week 24. The treatment effect of sotatercept on WHO FC improvement at week 24 was consistent across the post hoc subgroups stratified by baseline risk status.

Change From Baseline in PAH-SYMPACT Domain Scores

Patients in the sotatercept group reported greater improvements in both the physical impacts and the cardiopulmonary symptoms domain scores than those in the placebo group from baseline to week 24. For the physical impact domain, the difference between arms was −0.26 points (95% CI, −0.49 to −0.04) in favour of sotatercept. For the cardiopulmonary symptoms domain, the values were at −0.13 points (95% CI, −0.26 to −0.01) in favour of sotatercept. In both cases, negative values indicated improvement.

EQ-5D-5L Visual Analogue Score

Patients treated with sotatercept showed a greater increase in the European Quality of Life 5 Dimensions 5 Level (EQ-5D-5L) visual analogue score (VAS) compared to those receiving placebo. Specifically, there was an increase (improvement) in the VAS from baseline that was greater in the sotatercept group ([redacted]) than in the placebo group [redacted]

[redacted]). The difference between groups was [redacted] points ([redacted]) in favour of sotatercept.

PAH-Specific Hospitalization

Fewer hospitalizations were observed in the sotatercept group compared to the placebo group. This outcome was obtained from the composite end point of time to clinical worsening or death. Overall, 7 patients (4.4%) in the placebo group and 1 patient (0.6%) in the sotatercept group were hospitalized, with a risk difference of [redacted] in favour of sotatercept.

Harms Results

Through week 24, the most common AEs associated with sotatercept when compared to placebo included epistaxis (12.3% versus 1.9% respectively), telangiectasia (10.4% versus 3.1%), and dizziness (10.4% versus 1.9%). These events were mostly mild to moderate in severity. Serious AEs occurred in 14.1% of participants in the sotatercept group and 22.5% in the placebo group, with no significant patterns emerging. The sotatercept group had isolated instances of atrial flutter, falls, and hemoptysis, with only 2 SAEs (1 fall and 1 hemoptysis) deemed related to the study intervention. In contrast, the placebo group reported multiple cases of PAH, cardiac arrest, right ventricular failure, and dyspnea. No deaths were reported in the sotatercept group during the initial 24 weeks, compared to 6 deaths in the placebo group. By the final data cut-off, 2 deaths occurred in the sotatercept group.

The sotatercept group had a lower discontinuation rate due to AEs compared to the placebo group. Notably, telangiectasia incidents were higher in the sotatercept group but were neither serious nor severe, with only 1 case leading to treatment discontinuation. The sponsor identified several AEs of special interest, including increased hemoglobin, thrombocytopenia, and various bleeding events. Epistaxis was the most reported bleeding event (12.3%) in the sotatercept group, followed by gingival bleeding (3.1%). None of these bleeding events were serious or severe, though 2 participants discontinued treatment due to bleeding events. Increased hemoglobin levels were observed in 4.3% of participants in the sotatercept group, leading to study intervention interruption in 3 cases, but none were serious or severe. Thrombocytopenia was more common in the sotatercept group than the placebo group (6.1% versus 2.5%).

Critical Appraisal

Internal Validity

The STELLAR trial was a well-designed phase-3, multicentre, double-blind, randomized placebo-controlled study assessing the efficacy and safety of sotatercept versus placebo over 24 weeks in adult patients with PAH receiving stable background therapy. The trial used a robust 1:1 random allocation process, generated by a computer algorithm and centrally managed to maintain allocation concealment. Although blinding was effective initially, patients might have inferred their treatment group due to more frequent AEs like telangiectasia and nosebleeds in the sotatercept group. Adherence was meticulously monitored, with rates exceeding 98%, and deviations were well-documented. Missing data were handled appropriately through sensitivity analyses, which results agreed with primary analysis outcomes for key measures like 6MWD, NT-proBNP, PVR, and PAH-Symptoms and Impact Questionnaire (PAH-SYMPACT). Outcome

measurement methods were validated and reliable, and the reported outcomes and analysis plan adhered to the study protocol.

External Validity

The reimbursement criteria for sotatercept target patients with PAH receiving background therapy who do not meet low-risk status – defined by WHO FC I or II, a 6MWD of more than 440 m, and specific NT-proBNP or BNP levels.

Overall, the 323 patients in the STELLAR study were deemed representative of the population with PAH in Canada, though certain subgroups (e.g., HIV, portal hypertension) and demographics may not be properly represented. The STELLAR study enrolled 53 patients of 323 (16.4%) at low risk, which is an excluded patient population in the suggested reimbursement criteria and 157 patients (48.6%) within the FC II stratum. However, clinical experts we consulted considered that the impact on the generalizability of results was low and the effects were still applicable to the target population for reimbursement.

The trial's restriction to patients with a baseline PVR of at least 400 dyn·sec·cm^{-5} may not fully represent the broader population with PAH. Additionally, the 24-week median treatment duration and study design limit the ability to determine long-term mortality outcomes and extended safety profiles. Although the long-term data suggests that efficacy and harm outcomes remain similar to the STELLAR results.

GRADE Summary of Findings and Certainty of the Evidence

GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform our expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

Results of GRADE Assessments

The GRADE assessments included an evaluation of the main outcomes considered important by clinicians, patient groups, and committee members. The comparison evaluated in the GRADE assessments of this report were that of sotatercept against placebo. In Table 3 we present the GRADE summary of findings, respectively, for each comparison.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- mortality-deaths
- 6MWD
- multicomponent improvement
- time to first occurrence of clinical worsening event or death
- PVR
- NT-proBNP
- change in WHO FC
- HRQoL (PAH-SYMPACT physical impacts domain score and PAH-SYMPACT cardiopulmonary symptoms domain score and EQ-5D-5L)
- hospitalization (PAH specific)
- harms (AEs, serious AEs, AEs of special interest).

Table 3: Summary of Findings for Sotatercept Versus Placebo for Patients With PAH

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Placebo	Sotatercept	Difference (95% CI)		
Clinical efficacy							
Mortality Follow-up: median 24 weeks	323 (1 RCT)	NA	6/160 (3.8%)	2/163 (1.2%)		Low[a]	Sotatercept may reduce the number of deaths when compared with placebo. The clinical magnitude of the effect is unclear.
6MWD, change from baseline in metres Follow-up: median 24 weeks	323 (1 RCT)	NA	1.0 (range: −1.0 to 5.0)	34.4 (range: 32.5 to 35.5)		High[b]	Sotatercept results in a clinically important increase in 6MWD when compared with placebo.
Multicomponent improvement (6MWD and NT-proBNP level and WHO FC) Follow-up: median 24 weeks	321 (1 RCT)	NA	16/160 (10.1%)	63/163 (38.9%)		High[c]	Sotatercept results in an important increase in the proportion of patients with multicomponent improvement when compared with placebo.
Composite: time to clinical worsening or death. Follow-up: median 24 weeks	323 (1 RCT)	NA	42/160 (26.3%)	9/163 (5.5%)		High[c]	Sotatercept results in an important reduction in the proportion of patients with the composite end point when compared with placebo.
Pulmonary vascular resistance, median change from baseline in dyn·sec·cm^{-5} Follow-up: median 24 weeks	323 (1 RCT)	NA	32.8	−165.1 (95% CI, −184.0, −152.0)		High[d]	Sotatercept results in a decrease in pulmonary vascular resistance when compared with placebo. The clinical magnitude of the effect is unclear.[d]
NT-proBNP, change from baseline in pg/mL	323 (1 RCT)	NA	58.6	−230.3 (range: −236.0 to −233.0)		High[d]	Sotatercept results in a decrease in NT-proBNP when compared with placebo. The clinical

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Placebo	Sotatercept	Difference (95% CI)		
Follow-up: median 24 weeks							magnitude of the effect is unclear.[d]
Improvement in WHO FC Follow-up: median 24 weeks	322 (1 RCT)	NA	22/159 (13.8%)	48/163 (29.4%)	[redacted]	High[c]	Sotatercept results in an important increase in the proportion of patients with improvement in WHO FC when compared with placebo.
PAH-specific hospitalization Follow-up: median 24 weeks	323 (1 RCT)	NA	7/160 (4.4%)	1/163 (0.6%)	[redacted]	High	Sotatercept results in an important decrease in the proportion of patients hospitalized due to PAH when compared to placebo.
Health-related quality of life							
Health-related quality of life, PAH-SYMPACT, and EQ-5D-5L Follow-up: median 24 weeks	(1 RCT)	MD of change from baseline between sotatercept and placebo was −0.26 points (95% CI, −0.49 to −0.04) in the PAH-SYMPACT physical domain and of −0.13 (95% CI, −0.26 to −0.01) in the cardiopulmonary symptoms' domain (negative values mean improvement). For the EQ-5D-5L VAS, the MD was [redacted] points more in sotatercept [redacted] higher values mean improvement) in favour of sotatercept.[e]				Moderate[e]	Sotatercept likely results in an important improvement in health-related quality of life measurements (PAH-SYMPACT and EQ-5D-5L) when compared with placebo.
Harms							
Adverse events Follow-up: range 42 weeks to 72 weeks	323 (1 RCT)	NA	149/160 (93.1%)	151/163 (92.6%)	[redacted]	Low[f]	Sotatercept may result in little-to-no clinically meaningful difference in adverse events when compared with placebo.
Serious adverse events Follow-up: range 24 weeks to 72 weeks	323 (1 RCT)	NA	47/160 (29.4%)	40/163 (24.5%)	[redacted]	Low[f]	Sotatercept may result in little-to-no clinically meaningful difference in serious adverse events when compared with placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Placebo	Sotatercept	Difference (95% CI)		
Adverse events of special interest, telangiectasia and epistaxis Follow-up: range 24 weeks to 72 weeks	323 (1 RCT)	NA	7/160 (4.4%)	27/163 (16.6%)	[redacted]	High	Sotatercept results in an increase in the proportion of patients with events of telangiectasia or epistaxis when compared with placebo.

6MWD = 6-minute walk distance; CI = Confidence interval; EQ-5D-5L = EuroQol 5 Dimensions 5 Level; FC = functional class; MD = mean difference; MID = minimally important difference; NA = not applicable; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PAH = pulmonary arterial hypertension; PAH-SYMPACT = PAH-Symptoms and Impact Questionnaire; VAS = visual analogue score.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]Rated down 2 levels for imprecision. The 95% CI is wide and may include important effects of benefit but also the possibility of trivial effects. The study presents a low number of events. and it was not powered to detect a difference for this outcome. No MID or threshold of clinical significance was obtained; hence, the null effect was used for determining the target of the rating of certainty.

[b]Although the lower limit of the CI (27.5 m) is below the MID of 33 m, it was deemed patients and clinicians would consider this an important effect of benefit; hence, no rating down for imprecision was performed.

[c]Clinical experts considered that if 5 to 10 per 1,000 patients treated with sotatercept versus placebo improved (or got worse) it would be a meaningful beneficial (or harmful) effect; hence, no rating down for imprecision was performed.

[d]No MID was obtained for this end point. Clinical experts considered the lower change observed to be clinically meaningful.

[e]MIDs for the physical impacts and cardiopulmonary symptoms domains were estimated to be −0.3 and −0.2, respectively. Hence, values were rated down 1 level for imprecision because they include the threshold of the MID. No MID was obtained for the EQ-5D-5L VAS.

[f]May be little-to-no difference between groups, but the 95% CI is wide and includes a possible important reduction in total adverse events as well as an increase in adverse events, using a threshold of benefit-harm of 20 patients per 1,000 treated.

Source: Clinical Study Reports

Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

Description of Studies

The evaluation of long-term outcomes is supported by 3 key reports. First, the long-term assessment of AEs and description of efficacy outcomes of sotatercept were addressed during the LTDB treatment period of the STELLAR trial. Additionally, efficacy and safety end points were evaluated in the open-label extension (OLE) phase of the PULSAR phase II study. Lastly, the ongoing open-label SOTERIA trial provides primary evidence, though current information is based on interim analyses. Subsequent subsections will provide detailed descriptions of each study.

The primary objective of the STELLAR extension period was to evaluate the long-term incidence of AEs of sotatercept. After completing the 24-week DBPC treatment period, patients entered the LTDB treatment period lasting up to 72 weeks, eventually transitioning to the long-term follow-up study, SOTERIA, upon unblinding. Due to varying enrolment times in STELLAR, some participants had more visits beyond the initial 24 weeks. The PULSAR study, conducted from June 2018 to March 2022, also evaluated the safety and efficacy of sotatercept over a 24-week DBPC period followed by an 18-month OLE. SOTERIA, initiated in May 2021 and ongoing across 196 sites in 21 countries, aims to assess the long-term efficacy, safety, and tolerability of sotatercept up to 7 years.

Efficacy Results

STELLAR LTDB Study

The STELLAR LTDB study extended the evaluation of the long-term safety and efficacy of sotatercept beyond the initial 24-week DBPC phase. As patients transitioned into the SOTERIA study (those who completed the DBPC treatment period and were on treatment in the LTDB treatment period were eligible to participate in the open-label long-term follow-up study), the efficacy outcomes during the LTDB period remained descriptive, maintaining the positive trends seen at week 24. Sotatercept continued to show superior improvements in 6MWD, PVR, NT-proBNP levels, WHO FC, and the proportion of participants achieving a low-risk score compared to placebo.

PULSAR Study

The PULSAR study, a phase II trial, assessed the long-term efficacy and safety over a 24-week DBPC period followed by an 18-month OLE phase. Reductions in PVR were maintained from baseline to months 18 to 24 in both the continued sotatercept group and the placebo-crossed group. Improvements in 6MWD and NT-proBNP levels were also sustained in both groups. WHO FC improvements were notable, with a high percentage of patients achieving or maintaining FC II and some reaching FC I. Time to clinical worsening events was low and mortality risk scores reflected sustained low-risk status.

SOTERIA Study

The ongoing SOTERIA study, initiated in May 2021, focuses on the long-term efficacy, safety, and tolerability of sotatercept up to 7 years. At 1 year, patients maintained the improvements in 6MWD, NT-proBNP levels, WHO FC, and low-risk scores consistent with the STELLAR trial results. Clinical worsening events remained

low, with only 6.2% of participants in the continued sotatercept arm experiencing such events, and even fewer in the placebo-crossed group. Detailed results will become available as the study progresses.

Harms Results

STELLAR LTDB Study

The STELLAR LTDB study showed a consistent profile for the harm outcomes in the sotatercept arm compared to the initial 24-week analysis. Common AEs in the sotatercept group included epistaxis, telangiectasia, dizziness, nasal congestion, thrombocytopenia, and increased hemoglobin levels, primarily mild to moderate. The sotatercept group reported 2 deaths due to AEs, compared to 7 deaths in the placebo group. Discontinuation due to AEs was lower in the sotatercept group (3.7%) compared to the placebo group (6.9%).

PULSAR OLE Study

In the PULSAR OLE phase, all participants in the sotatercept 0.7 mg/kg group reported AEs, similar to those in the STELLAR study. Serious AEs related to the study drug were reported in 4.8% of participants, including conditions like fever, increased red blood cells, and systemic lupus erythematosus. Discontinuation due to AEs occurred in 19% of participants in the continued sotatercept 0.7 mg/kg arm, with 3 deaths reported, including 1 due to a brain abscess. AEs of special interest included leukopenia, neutropenia, and thrombocytopenia, occurring in 17.3% of participants. Hemoglobin increases and telangiectasia were noted, with the latter developing after approximately 1.5 years of treatment.

SOTERIA Study

In the SOTERIA study, 90.8% of participants experienced 1 or more AEs, with 3.5% discontinuing treatment and 2.8% dying due to AEs. Serious AEs occurred in 30.3% of patients, with telangiectasia reported in 17.4% of participants, none deemed serious. Epistaxis was the most common bleeding event (22.1%), with serious bleeding events occurring in 5.2% of participants. Increased hemoglobin levels were observed in 14.3% of participants, nonserious, and thrombocytopenia occurred in 6.1%, with 3 cases being serious and treatment related.

Critical Appraisal

The LTDB phase of the STELLAR study presented efficacy and harm end points descriptively due to patient attrition, as participants could transition to the SOTERIA trial. Blinding and randomization were maintained, though unblinding was possible due to AEs associated with sotatercept. The open-label PULSAR study, lacking a comparator, posed a higher risk of bias, potentially affecting patient expectations and reporting of patientive measures. Similarly, the ongoing SOTERIA study, also open-label and without a comparator, faced similar biases, with potential influences on patient-reported outcomes and the inclusion of patients with good drug performance.

The LTDB phase shared limitations with the pivotal STELLAR trial, particularly the exclusion of patients with certain types of PAH and the inclusion of both WHO FC II and III patients. Extended observation beyond 24 weeks helped confirm AEs, aligning with pivotal trial results. The PULSAR study included only WHO FC II and III patients, presenting similar limitations. Conducted at 43 centres in 8 countries, it

lacked representation in Canada, but clinical experts did not express concerns about generalizability from international evidence.

Indirect Comparisons

No indirect treatment comparison was submitted.

Studies Addressing Gaps in the Evidence From the Systematic Review

No studies addressing gaps in the evidence were identified.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with PAH who are not at low risk. Low risk is defined as: • FC I or II • 6MWD > 440 m • NT-proBNP < 300 ng/L or BNP < 100 ng/L.
Treatment	Sotatercept as an add-on to optimal BGT Optimal BGT is defined as: • patients receiving optimal number and doses of therapies according to clinical guidelines • patients may be receiving double or triple therapy depending on contraindications and/or tolerability of available PAH therapies.
Dose regimen	0.3 mg/kg for first dose, followed by 0.7 mg/kg every 3 weeks
Submitted price	Sotatercept 45 mg vial, $8,717.15 Sotatercept 60 mg vial, $11,622.87 Sotatercept 2 × 45 mg vials, $17,434.30 Sotatercept 2 × 60 mg vials, $23,245.73
Submitted treatment cost[a]	First year, per patient annual cost: $152,344 Subsequent years, per patient annual cost: $186,523
Comparator	Optimal BGT includes any combination of the following drugs: • sildenafil citrate and tadalafil (PDE5i), • bosentan, ambrisentan, and macitentan (ERA), • epoprostenol, treprostinil, and selexipag, (prostacyclin analogues).
Perspective	Canadian publicly funded health care payer

Component	Description
Outcomes	QALYs, LYs
Time horizon	Lifetime (30 years)
Key data sources	STELLAR trial COMPERA registry data
Key limitations	• The treatment effect of sotatercept on mortality, hospitalization, and prostacyclin analogue infusion escalation was overestimated in the submitted model. This was a result of double counting the effect of sotatercept on those outcomes by first modelling a reduction in patient risk status (which is associated with the likelihood of these clinical outcomes occurring), and then applying an additional benefit using a hazard ratio for those receiving sotatercept on the same clinical outcomes. There is insufficient evidence to suggest that treatment with sotatercept reduces the risk of mortality, hospitalization, and prostacyclin analogue infusion escalation in addition to the benefit of achieving a lower risk status. • The sponsor assumed that the treatment effect of sotatercept observed from weeks 12 to 24 in the STELLAR trial would persist indefinitely over a 30-year time horizon; however, the true duration of treatment effect of sotatercept is unknown. • The sponsor estimated mortality in the model based on data from a subgroup of patients from a European PAH registry who had no comorbidities. In Canada, it is anticipated that sotatercept would include patients with PAH who have comorbidities. • In the sponsor's submitted model, 29.6% of patients started in the low-risk health state and were able to receive treatment with sotatercept. However, the target population in this review excluded patients that are low risk.
CDA-AMC reanalysis results	• To account for the identified key limitations, we revised the way in which the treatment effect of sotatercept was included in the model and the population from which all-cause mortality was extrapolated. We were unable to address limitations associated with the duration of treatment effect for sotatercept. • In our base case, the ICER for sotatercept plus optimal BGT versus optimal BGT alone was $436,796 per QALY gained (incremental costs: $1,786,879; incremental QALYs: 4.09).

6MWD = 6-minute walk distance; BGT = background therapy; BNP = B-type natriuretic peptide; ERA = endothelial receptor antagonists; FC = functional class; ICER = incremental cost-effectiveness ratio; LY = life-year; NOC = Notice of Compliance; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PAH = pulmonary arterial hypertension; PDE5i = phosphodiesterase type 5 inhibitors; QALY = quality-adjusted life-year.

[a]The weighted average annual cost of sotatercept assumed by the sponsor was calculated based on the patients' weight distribution derived from the STELLAR trial to determine the use rates for each kit (45, 60, 2 × 45 or 2 × 60 mg). This distribution indicated that the use rates for the 45 mg, 60 mg, 2 x 45mg and 2 x 60mg vial kits are 44.73%, 48.38%, 6.88% and 0.01%, respectively.

Budget Impact

We identified the following key limitations with the sponsor's analysis: the definition of optimal background therapy is uncertain, the gradual uptake of treatment with sotatercept is inappropriate, and the uptake of sotatercept is uncertain. Our reanalysis revised the gradual initiation of sotatercept. In our base case, the 3-year budget impact of reimbursing sotatercept for the requested population is estimated to cost $284,952,390 ($62,051,571 in year 1, $94,650,189 in year 2, and $128,250,629 in year 3). Due to the uncertainty in the eligible population size and market uptake of sotatercept, we conducted scenario analyses to assess the impact of alternative assumptions on the expected budget impact of sotatercept. In these scenarios, the budget impact was sensitive to increases in the eligible population and faster uptake of sotatercept upon its potential listing; the 3-year budget impact of sotatercept increased by 12% and 22%, respectively, in these scenarios.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Danyaal Raza, Dr. Edward Xie, and Dr. Peter Zed

Meeting date: August 29, 2024

Regrets: One expert committee member did not attend.

Conflicts of interest: None

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.