NCPE Assessment

Technical Summary

Sotatercept (Winrevair®)

HTA ID: 24041

March 2026

Applicant: MSD HH Ireland

Sotatercept, in combination with other pulmonary arterial hypertension (PAH) therapies, for the treatment of PAH in adult patients with World Health Organisation (WHO) Functional Class (FC) II to III, to improve exercise capacity.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of sotatercept (Winrevair ®) when given in combination with other pulmonary arterial hypertension (PAH) therapies, for the treatment of PAH in adult patients with WHO Functional Class (FC) II to III, to improve exercise capacity.

Following assessment of the Applicant's submission, the NCPE recommends that sotatercept (Winrevair ®) not be considered for reimbursement for this indication.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (MSD HH Ireland) Health Technology Assessment of sotatercept (Winrevair®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In April 2025, MSD HH Ireland submitted a dossier on the comparative effectiveness, cost-effectiveness and budget impact of sotatercept (Winrevair®) in combination with other pulmonary arterial (PAH) therapies, for the treatment of PAH in adult patients with World Health Organisation (WHO) Functional Class (FC) II to III, to improve exercise capacity. MSD HH Ireland is seeking reimbursement of sotatercept on the High-Tech Drug Arrangement. At the time of the reimbursement application by the Applicant, sotatercept was licensed for use in patients with PAH and WHO FC II to III only. The sotatercept licence has subsequently been extended to a wider population of patients (i.e. to also include patients with PAH with WHO FC IV). The focus of this assessment is on the submitted population of patients with PAH and WHO FC II to III only.

Sotatercept is an activin receptor type IIA-Fc (ActRIIA-Fc) fusion protein. Activin signalling is overactive in patients with PAH, leading to increased pro-proliferative signalling that drives the pulmonary vascular remodelling underlying the PAH disease. Sotatercept is administered once every three weeks as a single subcutaneous (SC) injection according to patient weight. Treatment is initiated with a single dose of 0.3 mg/kg and after three weeks may be escalated to the recommended target dose of 0.7 mg/kg once every three weeks thereafter. The Summary of Product Characteristics (SmPC) does not specify a stopping rule for sotatercept. Treatment with sotatercept is therefore expected to be lifelong. The comparator for this assessment is standard of care with background therapies (BGTs) which is dependent on risk status. The NCPE consider this to be appropriate. Several drug classes of BGTs are reimbursed in Ireland including endothelin-1 receptor antagonists (ERA); phosphodiesterase-5 inhibitors (PDE-5i); prostacyclin pathway agents (PPA) and one soluble guanylyl cyclase stimulator (sGCS). In adult patients with PAH and WHO FC II, standard of care consists of dual oral therapy (ERA+PDE5i) in low-risk status, or triple therapy (ERA+PDE5i/sGC+PPA) in intermediate-low-risk status where PPA is administered as oral or inhaled therapy. In patients with WHO FC III, standard of care consists of triple therapy (ERA+PDE5i+PPA) in intermediate-high-risk status where PPA (e.g., treprostinil) is administered as a subcutaneous infusion. This was validated by clinical opinion to the Review Group.

1. Comparative effectiveness of sotatercept in combination with BGTs

The clinical efficacy and safety of sotatercept was assessed in the STELLAR trial; a multicentre, double-blind, phase III clinical trial in which adults with PAH (WHO FC II or III) were randomly assigned in a 1:1 ratio to receive subcutaneous sotatercept (n=163, starting dose, 0.3 mg/kg body weight; target dose, 0.7 mg/kg) or placebo (n=160) once every three weeks. All participants were required to be on stable BGT i.e., patient-specific dose goal for each therapy already achieved for at least 90 days prior to enrolment in STELLAR.

All primary and secondary efficacy endpoints were assessed at Week 24 (26 August 2022), except for time to clinical worsening or death which were assessed at the final analysis (06 December 2022).The median change from baseline at week 24 in the 6-minute walk distance was 34.4 meters (95% confidence interval [CI], 32.5 to 35.5) in the sotatercept group and 1.0 meters (95% CI, −0.3 to 3.5) in the placebo group. The Hodges–Lehmann estimate of the difference was 40.8 meters (95% CI, 27.5 to 54.1; P<0.001). Results demonstrated that for eight of the nine prespecified key secondary endpoints, more favourable outcomes were observed in the sotatercept group compared to the placebo group. These included the change from baseline to Week 24 in the following: multicomponent improvement, pulmonary vascular resistance (PVR), NT-proBNP level, improvement in WHO FC, the percentage of patients who achieved or maintained a low French risk score, and improvements in the PAH-SYMPACT (Physical Impacts and Cardiopulmonary Symptoms domains). Favourable outcomes for sotatercept versus placebo were also seen in the time to first occurrence of death or clinical worsening endpoint. No between group difference was observed in the PAH-SYMPACT (Cognitive or Emotional Impacts domain) from baseline to Week 24. The EQ-5D-5L was an exploratory endpoint. There was no difference in the change from baseline to Week 24 between arms for quality of life.

Key limitations of the STELLAR trial include:

- The majority of endpoints were assessed at 24 weeks, therefore comparative effectiveness beyond this timepoint is unknown.
- Due to low event numbers and limited duration of follow-up, the extent to which sotatercept will delay or prevent clinical worsening events, or lead to improvements in

mortality and morbidity over current standard of care, cannot be reliably determined.

- BGT was not provided as study medication during the STELLAR trial, and instead was provided to trial participants according to local practice in each treatment site. The dosage regimen for each BGT in STELLAR could not be verified by the Applicant.

2. Safety of **sotatercept**

The clinical safety of sotatercept was informed by the STELLAR trial. The safety analysis set was defined as all participants (n=323) who received at least one dose of study intervention. The median duration of treatment with sotatercept was 313 days and 273 days with placebo. Treatment emergent adverse events (TEAEs), considered related to the study intervention, occurred with a higher incidence in the sotatercept arm (41.1%) compared to the placebo arm (25.6%), respectively. These included telangiectasia (16.6% vs 4.4%), epistaxis (22.1% vs 1.9%), increased haemoglobin (8.6% vs 0.6%), and injection site erythema (3.1% vs 0.6%). Increases in haemoglobin and thrombocytopenia were managed by dose adjustments. Discontinuations of treatment due to telangiectasia occurred in 1% of the sotatercept group. No participant with telangiectasia suffered a serious bleeding event. The SmPC advises additional monitoring of haemoglobin and platelet count is recommended for the first five doses of sotatercept, or longer if values are unstable. Thereafter, counts should be verified every three to six months and the dose adjusted if necessary.

3. Cost effectiveness of sotatercept

The Applicant has compared the cost effectiveness of sotatercept plus BGT to BGT alone. Direct evidence was derived from the STELLAR trial.

Methods

Cost-effectiveness was assessed, from the perspective of the HSE, using a Markov cohort model implemented in Microsoft Excel®. The modelled population aligned with the licensed indication at the time of submission. The cost effectiveness model (CEM) comprised six mutually exclusive health states based on the European Society of Cardiology and the European Respiratory Society (ESC/ERS) guidelines 2022 four risk strata. These included low, intermediate-low, intermediate-high, and high-risk health states. The model also includes a post-lung/heart transplant state and a death state. Key concerns with the model structure are:

- The limited evidence to quantify the relationship between the model health states

(based on ESC/ERS 2022 risk strata) and key outcomes (including mortality, PAH-related hospitalisation, and quality-of-life).

- The external evidence and methodological approach used to estimate mortality by risk strata may not reliably predict survival. It is likely to overestimate differences in mortality between risk strata. This key model driver could not be addressed in the NCPE adjusted base case.

The treatment effects captured by the CEM were improvement or worsening in ESC/ERS risk strata, mortality, escalation of infused PPA utilisation, and PAH-related hospitalisation. The key efficacy inputs were the transition probabilities between risk states (up to Week 24) and relative effect estimates for risk strata. Treatment discontinuation was not included in the Applicant's base case. Due to limited follow-up time in STELLAR, the long-term effects of sotatercept is not known. A gradual treatment waning effect was applied over a 100 year period starting from Week 24. The Review Group believe that sotatercept benefits will likely wane over time, but note that there is no evidence available to inform the time frame over which this will occur. Health-related quality of life utility estimates were informed by EQ-5D-5L data, collected in the STELLAR trial and mapped to the EQ-5D-3L using the Hernandez-Alava- algorithm. Age-related utility decrements were applied. Disutilities associated with adverse events and PAH-related hospitalisations were included. Costs and resources included were drug and administration costs, adverse-event costs and health state specific disease management costs. A once-off, end-of-life cost was also included.

Several changes were made to inform the NCPE adjusted base case. These included the removal of additional treatment effects which double-count the benefit of sotatercept in reducing mortality, PAH-related hospitalisations, and escalation of infused PPA utilisation. These benefits are captured by transitions between risk strata. Further changes included updating the PPA maintenance dose for treprostinil to align with clinical opinion, correcting errors in the calculation of certain disutilities, and the removal of utility increments for PPA infusions (which are already accounted for in the health-state utility values).

Results

Results of the Applicant base case deterministic cost-effective analysis are presented in Table 1.

Table 1: Applicant base case incremental cost-effectiveness results [a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
BGT only	488,582	2.99	-	-	-
Sotatercept + BGT	2,445,279	7.94	1,956,697	4.94	395,767

BGT: background therapy; **ICER:** incremental cost-effectiveness ratio**; QALY:** quality-adjusted life years

[a] Corresponding probabilistic ICER using 1,000 iterations =€410,767/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes.

Results of the NCPE adjusted base case are presented in Table 2.

Table 2: NCPE adjusted base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
BGT only	557,878	3.45	-	-	-
Sotatercept + BGT	2,048,622	6.70	1,490,743	3.25	458,744

BGT: background therapy; **ICER:** incremental cost-effectiveness ratio**; NCPE:** National Centre for Pharmacoeconomics**; QALY:** quality-adjusted life years

[a] Corresponding probabilistic ICER using 1,000 iterations =€483,008/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes.

Sensitivity analysis

Based on the deterministic one-way sensitivity analysis using the Applicant and NCPE adjusted base case, the most influential parameters were the relative risks for worsening and improving between Week 12 to 24, and the relative risk for escalation of infused PPA utilisation. Three key scenario analyses of the NCPE adjusted base case were undertaken: treatment waning (at 5, 15 and 30 years), treatment discontinuation (patients who worsen within the first 24 weeks of treatment discontinue sotatercept and follow BGT transitions) and excluding low-risk patients at baseline. For all scenarios, sotatercept (plus BGT) was not cost-effective, at a €45,000 per QALY threshold.

A price-ICER analysis, conducted using the NCPE-adjusted base case, demonstrated that sotatercept (plus BGT) could not achieve cost-effectiveness, at a €20,000 per QALY or €45,000 per QALY threshold, at any discount.

4. Budget impact of sotatercept

The price to wholesaler per kit containing single vials of sotatercept 45mg or 60mg is €6,393.15 and €8,524.20 respectively. The price to wholesaler per kit containing two vials of sotatercept 45mg is €12,786.30. The estimated total cost of sotatercept per patient per year is €172,223.

The Applicant used several sources to inform the eligible patient estimates, including the published literature and clinical opinion. The Applicant estimates that approximately 13 patients will be newly diagnosed with PAH, in Ireland each year. The Applicant assumes there will be 233 (total adult prevalent) patients in Year One, increasing to 251 patients in Year Five. The Applicant estimates that 58% of the PAH patient population will be eligible for treatment with sotatercept; reflecting those with WHO FC II or III who are on double or triple PAH directed BGT. The Applicant assumes that 40% of the eligible population in Year One rising to 45% in Year Two and beyond would be treated with sotatercept plus BGT in clinical practice. This was validated by clinical opinion to the Applicant. Costs of BGTs have been omitted from the budget impact model as sotatercept is considered an add-on therapy to BGT. The Applicant's estimated five-year cumulative drug budget impact for sotatercept is €50.43 million (including VAT).

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

6. Conclusion

The NCPE recommends that sotatercept (when given in combination with BGT), for this indication, not be considered for reimbursement. *

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.