SMC2831

sotatercept powder and solvent for solution for injection (Winrevair®)

Merck Sharp & Dohme (UK) Limited

16 January 2026

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

sotatercept (Winrevair®) is not recommended for use within NHSScotland.

Indication under review: 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.

In a phase III study of patients with PAH with WHO FC II or III who were receiving stable background therapy, sotatercept significantly improved exercise capacity, measured by the 6-minute walk test, compared with placebo.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

The submitting company has indicated their intention to make a resubmission.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Sotatercept is an activin signalling inhibitor that is highly selective for Activin-A. Levels of Activin-A are increased in pulmonary arterial hypertension (PAH) which causes an increase in pro-proliferative and decrease in antiproliferative signalling pathways. This results in vascular cell hyperproliferation and leads to increased pulmonary artery pressure and right ventricular dysfunction. Sotatercept rebalances these signalling pathways which modulates vascular proliferation.[1]

Sotatercept is administered once every 3 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 3 weeks may be escalated to the recommended target dose of 0.7 mg/kg. See the Summary of Product Characteristics (SPC) for additional details.[1]

1.2. Disease background

PAH is a rare and progressive condition of increased blood pressure in the arteries of the lungs. It is caused by the overexpression of vasoconstrictors (for example, endothelin-1) and underproduction of vasodilators (for example, nitric oxide and prostacyclin), the proliferation of endothelial and smooth muscle cells, and thrombosis. This causes progressive pulmonary vascular remodelling and increased resistance which increases pulmonary artery pressure, leading to right-sided heart failure and eventually death. Common symptoms are non-specific and include dyspnoea on exertion, fatigue and peripheral oedema; some patients may also experience chest pain. Syncope can develop as the disease progresses, and heart failure worsens. Risk factors include family history, female sex, presence of bone morphogenetic protein receptor 2 (BMPR2) mutations and use of appetite suppressants. The disease can restrict physical activity and affect quality of life. Long-term prognosis is poor with an estimated survival of 5 to 7 years in half of patients. World Health Organisation (WHO) classification of functional status (FC) ranges from I to IV based on the impact of symptom burden on physical activity and is used to predict survival and indicate a worsening in disease.[2-4]

1.3. Company proposed position

The submitting company had requested that sotatercept is restricted for use in patients with intermediate-low risk status on the European Society of Cardiology (ESC)/European Respiratory Society (ERS) four-strata risk rating system.

1.4. Treatment pathway and relevant comparators

In Scotland, the treatment pathway for PAH is reflective of ESC/ERS guidelines and is based on estimated risk of one-year mortality at diagnosis (three-strata rating) and follow-up (four-strata rating). The aim of treatment is to achieve and maintain a low risk status (estimated one-year mortality risk <5%). The factors used to calculate risk status include WHO Functional Class (FC), 6-minute walk distance (6MWD) and NT-proBNP. At diagnosis, ESC/ERS guidelines recommend double therapy for low or intermediate risk patients which includes an endothelin receptor antagonist (ERA) (for example, bosentan, ambrisentan or macitentan) and a phosphodiesterase 5 inhibitor (PDE5i) (for example, sildenafil or tadalafil). High risk patients are recommended triple

therapy with the addition of an intravenous (IV) or SC prostacyclin pathway agent (PPA) (for example, epoprostenol or treprostinil). At follow-up, low risk patients continue initial therapy, intermediate-low risk patients can add an oral PPA (for example, selexipag) or stop the PDE5i and add a soluble guanylate cyclase (sGC) stimulator (for example, riociguat) and intermediate-high or high risk patients can add an IV or SC PPA (if not already on triple therapy) and may be evaluated for lung transplant. A recent update to the treatment algorithm also recommends an inhaled PPA (for example, iloprost) as an option for intermediate-low risk patients and an activin signalling inhibitor (for example, sotatercept) in intermediate-low, intermediate-high or high risk patients. Patients may also receive supportive pharmacological (for example, diuretics) and non-pharmacological treatment (for example, rehabilitation programmes).[2, 4, 5]

Selexipag has been accepted by SMC for restricted use in patients with WHO FC III (SMC1235/17). Iloprost has been accepted for restricted use by SMC in patients with New York Heart Association Class III primary pulmonary hypertension (SMC219/05). Riociguat is accepted by SMC for restricted use as monotherapy as an alternative to an ERA (SMC1056/15). Based on the proposed positioning in intermediate-low risk patients, clinical experts indicated that selexipag in combination with an ERA and PDE5i is the most relevant comparator for this submission.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of sotatercept for the indication under review comes from the phase III STELLAR study.[3]

Table 2.1. Overview of relevant studies

Criteria	STELLAR[2, 3, 6]
Study design	A multicentre, randomised, double-blind, phase III study.
Eligible patients	• Aged ≥18 years with confirmed diagnosis of PAH (including idiopathic PAH, hereditary PAH, drug-induced PAH, connective-PAH and PAH associated with post shunt correction) with symptomatic PAH classified as WHO FC II or III • Stable background PAH therapy and diuretics ≥90 days prior to screening • 6MWD ≥150 and ≤500 metres repeated twice at screening and both values within 15% of each other
Treatments	Every 21 days via SC injection: • sotatercept at a starting dose of 0.3 mg/kg at visit 1 and escalated to a target dose of 0.7 mg/kg at visit 2, or • placebo Protocol approved dose modifications were permitted. Patients continued background monotherapy, double therapy or triple therapy with their standard PAH therapy which could consist of: ERA, PDE5i, sGCS, and prostacyclin analogues or receptor agonists. The double-blind placebo-controlled treatment period continued for 24 weeks and was followed by a long-term double-blind treatment period of up to 72 weeks. When the last patient completed the 24-week double-blind placebo-controlled treatment period, the study was unblinded and patients could roll over into the long-term follow-up study (SOTERIA).

Randomisation	Patients were randomised equally and stratified according to WHO FC (II versus III) and background PAH therapy (monotherapy or double therapy versus triple therapy).
Primary outcome	Change from baseline at week 24 in the 6MWD.
Secondary outcomes	The change from baseline at week 24 was assessed for secondary outcomes. These were tested hierarchically in the following order: 1. Multicomponent improvement measured by the proportion of patients achieving improvement in all three of the following criteria: • 6MWD increase ≥30 metres • NT-proBNP level decrease of ≥30% or maintenance or achievement of <300 pg/mL • Improve WHO FC or maintain WHO FC II 2. Change in PVR. 3. Change in NT-proBNP levels. 4. Improvement in WHO FC 5. Time to first occurrence of death or non-fatal clinical worsening event (worsening-related listing for lung or heart–lung transplantation, initiation or rescue therapy or increase in the prostacyclin dose by ≥10%, atrial septostomy, hospitalisation for worsening of PAH, or worsening of PAH relative to baseline as defined by both a worsened WHO FC and a decrease in 6MWD by ≥15%). 6. Achievement of a low French risk score at week 24 (all three criteria met: WHO FC I or II, 6MWD of >440 metres and NT-proBNP level of <300 pg/mL). 7-9. Physical impacts domain score, Cardiopulmonary symptoms domain score and, Cognitive/emotional impacts domain score of the PAH-SYMPACT questionnaire.
Statistical analysis	A hierarchical statistical testing strategy was applied in the study (in the order listed above), with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Efficacy analyses were performed in the intention-to-treat population, which included all patients who underwent randomisation. Safety analyses were performed in all patients who had received at least one dose of study medicine.

Abbreviations: 6MWD = 6-minute walk distance; ERA = endothelin receptor antagonist; FC = functional class; NT-proBNP = PAH = pulmonary arterial hypertension; PAH-SYMPACT = Pulmonary Arterial Hypertension–Symptoms and Impact; PCWP = pulmonary capillary wedge pressure; PDE5i = phosphodiesterase 5 inhibitor; PVR = pulmonary vascular resistance; RHC = right heart catheterisation; SC = subcutaneous; sGCS = soluble guanylate cyclase stimulators WHO = World Health Organisation

In STELLAR, the addition of sotatercept to stable background PAH therapy resulted in significant improvements in the primary outcome and in most hierarchically tested secondary outcomes. The results from the August 2022 data cut-off are presented in Table 2.2.[2, 3]

Table 2.2. Results from the primary analysis of the STELLAR study in the ITT population at week 24[2, 3]

	Sotatercept (n=163)	**Placebo (n=160)**
Primary outcome: Change in 6MWD from baseline at week 24, metres[a]		
Baseline	397.6	404.7
Median change	34.4	1.0
Median of all paired differences (95% CI)	40.8 (27.5 to 54.1), p<0.001	

Multicomponent secondary outcome measured from baseline at week 24[a]		
Improvement of WHO FC or maintenance of WHO FC II		
Yes, % (n/N)	71% (115/163)	52% (82/159)
Improvement in NT-proBNP by ≥30% or maintenance or achievement of level <300 pg/mL		
Yes, % (n/N)	85% (138/162)	40% (64/159)
Improvement in 6MWD by ≥30 metres		
Yes, % (n/N)	53% (87/163)	22% (35/159)
Improvement in all three criteria		
Yes, % (n/N)	39% (63/162)	10% (16/159)

Abbreviations: 6MWD = 6-minute walk distance; CI = confidence interval; FC = functional class; ITT = intention-to-treat; NT-proBNP = N-terminal pro B-type natriuretic peptide; WHO = World Health Organisation. [a]Statistically significant difference between sotatercept versus placebo.

Sotatercept was also associated in statistically significant improvements compared with placebo in the following secondary outcomes from baseline to week 24: change in pulmonary vascular resistance, change in NT-proBNP levels, change in WHO functional class, time to clinical worsening and maintaining or achieving a low French risk score.[3]

2.2. Evidence to support the positioning proposed by the submitting company

Subgroup analysis in patients with baseline ESC/ERS intermediate-low risk

The submitting company provided a post hoc subgroup analysis of patients in the STELLAR study who had ESC/ERS intermediate-low risk status at baseline. The results (considered confidential by the company) were broadly similar to the primary analysis.[7]

STELLAR within-trial analyses–comparison of sotatercept and selexipag

The submitting company provided a Bucher indirect treatment comparison (ITC) to compare sotatercept with selexipag but were unable to perform a comparison for the outcome of change in baseline risk status. Therefore, a post hoc within-trial analysis compared patients in the sotatercept group who were on double therapy with a PDE5i and ERA at baseline with patients in the placebo group who were on triple therapy with a PDE5i, ERA and selexipag at baseline. Based on the proposed positioning, the submitting company expect sotatercept to be used in patients with ESC/ERS low-intermediate-low risk status and in this population the most relevant comparator is triple therapy with a PDEi, ERA and selexipag. The results were considered confidential by the company.[7]

2.3. Health-related quality of life outcomes

Health-related quality of life (HRQoL) was assessed using the Pulmonary Arterial Hypertension–Symptoms and Impact (PAH-SYMPACT) questionnaire and EQ-5D-5L visual analogue scale (VAS) and utility index. PAH-SYMPACT is a disease-specific instrument that measures cardiopulmonary symptoms, physical impacts and cognitive/emotional impacts. The score for each domain ranges from 0 to 4 with higher scores corresponding to more severe symptoms or impacts; no minimal clinically important difference has been established.

The median change from baseline at week 24 was greater in the sotatercept group compared with placebo in PAH-SYMPACT physical impacts domain score (-0.13 versus 0.01, p=0.01) and cardiopulmonary symptoms domain score (-0.12 versus -0.01, p=0.028); the median treatment

difference between groups for both hierarchically tested outcomes was statistically significant. There was no median change in either group or no significant between group difference in PAH-SYMPACT cognitive/emotional impacts domain score from baseline at week 24.[2, 3]

There were no notable differences between groups for change in EQ-5D-5L utility index score from baseline at week 24 but an improvement was noted in the 100 point VAS in favour of sotatercept. The mean change from baseline at week 24 in the VAS was 4.33 in the sotatercept group versus -0.87 in the placebo group.[2, 3, 6]

2.4. Supportive studies

SOTERIA is an open-label follow-up study to assess the long-term safety and efficacy of sotatercept for up to 7 years in patients receiving stable background therapy for PAH. Patients were recruited from five parent studies including STELLAR and all received sotatercept SC every 21 days.[8]

The mean duration of treatment in SOTERIA was 448 days; 94% of patients had completed to week 24, 89% to year 1 and 13% to year 2. In patients that crossed over from the placebo group in the parent study and initiated sotatercept in SOTERIA (n=143), improvements from baseline to week 24 in the key outcome measures were similar to those seen in the sotatercept group in the STELLAR study. These improvements were maintained at 1 year. In patients that had received sotatercept in the parent study and continued to receive sotatercept in SOTERIA (n=259), the treatment effect on 6MWD, NT-proBNP levels, WHO FC I or II and low French risk score were similar at baseline, week 24 and 1 year.[8]

2.5. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence versus selexipag, the submitting company presented a Bucher ITC and a Matching-Adjusted Indirect Comparison (MAIC), as detailed in Table 2.3.

Table 2.3. Summary of indirect treatment comparison

Criteria	Overview
Design	Bucher ITC and MAIC
Population	Adult patients with PAH
Comparators	Selexipag (with or without background PAH therapy)
Studies included	STELLAR[3], GRIPHON[9] and TRACE[10]
Outcomes	WHO FC improvement, WHO FC worsening, change in 6MWD, change in NT-proBNP, time to death or non-fatal clinical worsening, time to death, time to PAH-related death and time to first PAH hospitalisation.
Results	For the Bucher ITC, sotatercept had better efficacy than selexipag for all outcomes except WHO FC improvement, time to death and time to PAH-related death as the 95% confidence intervals crossed 1, suggesting there was no evidence of a difference in efficacy. The MAIC identified similar results. The results for both ITCs were considered confidential by the company.

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

The STELLAR study provides evidence of the relative safety of sotatercept compared with placebo in combination with stable background PAH medicines. At the December 2022 data cut-off, including data from double-blind placebo-controlled period and long-term double-blind period, the median duration of treatment was 313 days in the sotatercept group and 273 days in the placebo group. Any treatment-emergent adverse event (AE) was reported by 93% (151/163) of patients in the sotatercept group and 93% (149/160) of patients in the placebo group, these were considered treatment related in 51% and 28%. A serious AE was reported in 24% versus 29% of patients in each group respectively. During the 24 week double-blind period, the proportion of patients with a dose reduction in each group was 6.1% versus 1.9%, dose delay was 7.4% versus 3.1% and patients discontinuing therapy due to an AE was 3.7% versus 6.9%.[2, 3]

The most frequently reported treatment-emergent AEs of any grade with an incidence >10% in the sotatercept group versus the placebo group were: COVID-19 (29% versus 26%), headache (24% versus 18%), epistaxis (22% versus 1.9%), telangiectasia (17% versus 4.4%), diarrhoea (15% versus 10%), dizziness (15% versus 6.3%), fatigue (14% versus 10%) and nausea (14% versus 12%).[2, 3]

Bleeding events were more commonly reported in the sotatercept group compared with placebo (35% versus 16%), mainly due to epistaxis. Serious bleeding events, including intracranial and gastrointestinal bleeding, occurred in 4.3% and 1.3% in the sotatercept and placebo groups respectively. Risk factors include concomitant use of prostacyclin analogues with or without anticoagulants, and thrombocytopenia which was also more frequent in the sotatercept group (10% versus 3.1%). Increased haemoglobin was also more common in the sotatercept group compared with placebo (8.6% versus 0.6%), no events were considered serious or severe. The SPC provides guidance on monitoring haemoglobin and platelet counts on initiation and during treatment.[1-3] The safety profile of sotatercept in SOTERIA was consistent with that reported in STELLAR.[8] Overall, sotatercept was considered well-tolerated and had a manageable safety profile.[2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the phase III STELLAR study, the addition of sotatercept to stable background PAH therapy resulted in a statistically significant median improvement of 40.8 metres in the 6MWD compared with placebo at 24 weeks. This improvement in exercise capacity was considered clinically relevant by the regulator.[2, 3]
- Sotatercept was associated with significant improvements when compared with placebo in supportive secondary outcomes including pulmonary vascular resistance (PVR), NT-proBNP levels, WHO FC, time to clinical worsening or death and the proportion that achieved or maintained a low French risk score at 24 weeks. There were also significant improvements in HRQoL assessed by PAH-SYMPACT, including physical impacts and cardiopulmonary symptoms.[2, 3]

- The results from the open-label, long-term follow-up SOTERIA study indicate that clinical benefits associated with sotatercept in 6MWD, NT-proBNP, WHO functional status and low French risk score were maintained for up to 1 year after finishing a parent study.
- Sotatercept is the first activin signalling inhibitor licensed for the treatment of PAH.[1, 2]

4.2. Key uncertainties

- STELLAR provides short-term evidence for sotatercept compared with placebo, and longer term evidence of efficacy and safety is limited to 1 year of further data from SOTERIA after patients completed their parent study. This is relevant as PAH is a chronic, progressive condition. The SOTERIA study is ongoing and additional results are awaited.[8]
- Based on the proposed positioning, selexipag in combination with a PDE5i and ERA is a relevant comparator however there is limited direct comparative evidence versus sotatercept. The submitting company conducted a Bucher ITC which was associated with several limitations. The population was broader than the positioning as it was not selective for ESC/ERS intermediate-low risk and not all patients were on background PAH therapy with a PDE5i and ERA. There were differences in study design (including sample size and outcomes reported) and baseline characteristics (including PAH subtype, time since diagnosis and background PAH therapy). The confidence intervals around the point estimates were wide, some outcomes included a small number of events and no safety or HRQoL outcomes were compared. Due to these limitations, the results were highly uncertain. The company also provided a MAIC which was the preferred approach, this was also associated with uncertainties. The results were broadly consistent with the Bucher ITC.
- The ITC was unable to provide a comparison for sotatercept versus selexipag for change in risk status. Therefore, the submitting company presented a post hoc within-trial analysis from STELLAR comparing patients taking a PDE5i plus ERA from the sotatercept group with those taking a PDE5i plus ERA plus selexipag from the placebo group. However, the results for this comparison are uncertain as randomisation has been broken resulting in different group sizes (both small in number) and imbalances in baseline characteristics that may favour sotatercept. These include patients in the sotatercept group having a shorter time since PAH diagnosis, a higher proportion considered low risk at baseline and on less intensive PAH background therapy. Also, as patients were stable on background PAH therapy at baseline, the comparison is unable to reliably measure additional change in risk status caused by selexipag in the placebo group. These limitations make the results very uncertain and they may not be appropriate to consider when trying to understand the relative efficacy of sotatercept and selexipag.[7]
- The submitting company provided results from a post hoc subgroup analysis of patients from the STELLAR study with an ECS/ERS intermediate-low risk at baseline.[7] Although this matches the proposed positioning, the analyses was not pre-planned and the study was not powered to detect differences between subgroups. The results from this subgroup have not been used in the economic analysis.
- There were some external validity issues with STELLAR that may affect the generalisability of study results to Scottish practice. Patients were receiving stable background PAH

therapy when sotatercept was initiated. However, this may not be reflective of patients who require treatment escalation because they have failed to achieve an adequate response on their current background therapy. The study excluded patients diagnosed with HIV-associated PAH, PAH associated with portal hypertension, schistosomiasis-associated PAH and pulmonary veno-occlusive disease and therefore there is limited evidence in these patients. Patients with PAH associated with connective-tissue disease, congenital heart disease, or drugs and toxins were underrepresented.[2, 3] These uncertainties may affect the generalisability of study results to Scottish patients.

- There were some limitations with the study methodology: dose modifications and monitoring was stricter in STELLAR than advised in the SPC which could potentially affect magnitude of benefit; known side effects such as telangectasia, bleeding events and haematological changes could have caused unintentional study unblinding; there were differences in the definition of time to clinical worsening between the study and regulatory guidance which was not fully adjusted in post hoc analysis; and mortality was not included as a separate outcome as advised by the European regulator to exclude a detrimental effect.[2, 3]

4.3. Clinical expert input

Clinical experts considered that sotatercept fills an unmet need and is a therapeutic advance due to the novel mechanism of action and clinical benefits demonstrated in the clinical trial programme.

4.4. Service implications

In Scotland, PAH is managed centrally at the Scottish Pulmonary Vascular Unit (SPVU). Scottish experts did not anticipate significant service implications with the introduction of sotatercept. Treatment will be initiated at a nurse led clinic and when the patient can self-administer, sotatercept will be administered at home. Blood monitoring can be conducted remotely, and patients will be reviewed every 3 months at the SPVU.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified patient group.

- We received a patient group submission from the Pulmonary Hypertension Association UK, which is a registered charity.

- Pulmonary Hypertension Association UK has received 5% pharmaceutical company funding in the past two years, including from the submitting company.

- PAH has a huge impact on day-to-day life. Despite receiving the best available treatments, many patients remain limited in their functional capacity. A survey conducted by the patient group showed the most impactful daily symptoms reported by patients were breathlessness during everyday activities, fatigue and tiredness.

- An unmet need remains in PAH: even with modern treatments, many people continue to live with substantial symptoms and functional limitation (often WHO FC II to III) and a high day-to-day burden. Survey work by the patient group shows that best available care still leaves many people struggling.

- Sotatercept is a potentially important advance: as a first-in-class therapy with very encouraging trial outcomes, it may represent a meaningful step-change for people who remain symptomatic despite current therapies. Experiences from the UK early access programme suggest that the clinical trial outcomes are reflected in the more complex clinical environment.

- Initiation requires hospital attendance every 3 weeks for the first 4–5 injections; ongoing dosing is self-administered every 3 weeks. This may affect travel and support needs. However, research conducted by the patient group showed that 92% of patients would prefer to travel longer distances to a specialist PAH centre than to be under the care of a non-PAH specialist at a more local hospital.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The company conducted an economic analysis, as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	30 years (lifetime)
Population	The submission focused on a subset of the medicine's marketing authorisation, specifically patients with intermediate-low risk status on the ESC/European Respiratory Society (ERS) four-strata risk rating system.
Comparators	The primary comparator for the economic analysis was selexipag. Both treatment arms were assumed to be taken in combination with background dual therapy, ERA and PDE5i. Patients in either arm could escalate to IV/inhaled PPA as a subsequent treatment therapy if they progressed to intermediate-high- or high-risk states (dependent on the treatment arm). The PPA subsequent treatments included epoprostenol, treprostinil and iloprost.
Model description	The company built a deterministic cohort model with: a. a short-term decision tree to capture events during the STELLAR study 24-week period, followed by b. a Markov state-transition model for the long-term horizon Both the decision tree and the Markov model utilise the ESC/ERS four-strata risk categories (low risk, intermediate-low risk, intermediate-high risk and high risk) as health states. The model also includes a death absorbing state and a post-transplant health state following a heart or lung transplant. It was assumed in the model that only patients with intermediate-high- and high-risk status would be eligible for a transplant. A stopping rule was modelled at the end of the 24 weeks, so that inadequate sotatercept responders in any health state discontinued treatment. After the first 24 weeks, patients in the sotatercept arm were assumed to remain on treatment until progression into the high-risk

	health state, where sotatercept is discontinued and patients are escalated to subsequent PPA treatment. Patients in the selexipag arm discontinued treatment in the intermediate-high and high-risk states, then escalate to subsequent treatment. It was assumed that upon discontinuation, all patients continued to receive dual background therapy until death.
Clinical data	The primary source of clinical data used in the economic model was sourced from STELLAR, which was used to inform baseline characteristics, the ESC/ERS risk-state transitions over 24 weeks and the 24-week stopping rule for inadequate sotatercept response. The comparative effectiveness estimates for sotatercept versus selexipag were derived from a subgroup of patients within the STELLAR trial. This within-trial analysis population included patients on background therapy and sotatercept versus patients on background therapy and selexipag (as part of their background therapy) plus placebo. An assessment of improvement and worsening of risk status using the ESC/ERS simplified four-strata risk-assessment tool was used to inform the relative risk effect of PDE5i, ERA plus sotatercept compared to placebo plus PDE5i and ERA plus selexipag. An ITC was conducted, as described in section 2.5, but the ITC was not used to determine the impact of treatment on risk status change associated with selexipag, compared to sotatercept. The ITC approach was used to determine the hazard ratio of PAH hospitalisation for those being treated with sotatercept vs selexipag. No adverse events were included in the model.
Extrapolation	Transition probability parameters for sotatercept arm were sourced from entire population of STELLAR. The short-term (decision-tree) transition probabilities were based directly on the transitions from baseline to 24 weeks. The long-term transition probabilities (Markov model) were based on week 12-24 data and continued until the end of the time horizon. It was assumed that the long-term transition probabilities would remain constant over time for the remainder of the model time horizon. No transitions were observed from intermediate-high to high risk in STELLAR for the sotatercept arm, so a proxy was applied using transitions from the FC III category, to allow transitions from intermediate-high to high risk. For selexipag, transition probabilities were derived by applying the Risk Ratio (RR) of improvement or worsening based on within-trial analysis to the sotatercept transition probabilities. Upon discontinuation of either treatment, the transition probabilities between the low risk and intermediate-low risk health states to the intermediate-high risk health state were sourced from the placebo arm of the STELLAR study. From the intermediate-high to high risk states (for off-sotatercept and selexipag) the transitions were sourced from Roman et al 2012.[11]
Quality of life	Health state utility values were derived from EQ-5D-5L data from STELLAR, mapped to ED-5D-3L using a crosswalk algorithm.[12] Utilities were calculated by ESC/ERS risk stratum using pooled recorded across treatment arms at baseline to week 24, and adjusted for age. Disutilities for administration route were applied to intravenous administration (-0.307) sourced from Davis et al 2018. No other disutility's were applied for different administration routes.[13]

	A one-off disutility (-0.105) was applied for both PAH Hospitalisation events and lung/heart transplantations. This was sourced from McMurray et. al (2018).[14] Additionally, a carer utility was presented by modelling gains in the lower-risk states by multiplying patient utility gain (relative to the high-risk state) by 0.123, sourced from Pennington et al. 2025. [15]
Costs and resource use	Costs included medicine acquisition for sotatercept, background therapy, selexipag and subsequent treatment therapies, resource use, administration and monitoring costs. Proportions of subsequent treatment therapies were sourced from a NHS 2024 PAH audit.[16] The model also included one-time costs for clinical progression events, which were hospitalisation, transplantation and death. No adverse events costs were modelled.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. A PAS discount is in place for selexipag and macitentan and these were included in the results used for decision-making by using estimates of the comparator PAS price.

6.2. Results

SMC considered results for decision-making that took into account all relevant PAS. SMC is unable to present these results due to competition law issues.

The primary cost driver was medicine acquisition costs. This was partially offset by the higher healthcare resource use costs for the selexipag arm, because more patients escalated to IV PPA treatment, which had a high medicine acquisition, administration, monitoring and consumable costs. The majority of QALY gains were accrued after 24 weeks, so the incremental benefit was driven almost entirely by modelled long-term extrapolation rather than study observation. Sotatercept generated more QALYs in the low, intermediate-low and intermediate-high risk states. In contrast, selexipag accumulated more QALYs in the high-risk state. A disutility for IV PPA treatment drove the selexipag QALYs down as selexipag patients escalated to PPA earlier than sotatercept (due to differences in efficacy and discontinuation criteria between arms).

6.3. Sensitivity analyses

Sensitivity analysis included probabilistic, deterministic and scenario analysis. The deterministic sensitivity analysis showed that the three parameters that have the greatest impact on the results are the proportion of selexipag patients receiving epoprostenol in high risk, in intermediate-high risk, and the RR of risk status worsening between sotatercept and selexipag.

Table 6.2 describes some selected scenario analyses.

Table 6.2 Key scenario analysis

#	Parameter	Base case	Scenario
1	Efficacy	HR of hospitalisation from Bucher ITC	Hospitalisation HR = 1
2		no further improvement in risk status beyond week 24	Allowing for one-cycle improvement of sotatercept patients upon initiating parenteral PPA
3		ESC/ERS risk strata health states	Relative risk of improvement and worsening from WHO FC ITC
4			Comparative effectiveness of sotatercept vs selexipag using the MAIC
5	Mortality		dependent model using Gompertz

6		Dependent model using Gamma	dependent model using Weibull
7		Data source for KM curves by risk: Rosenkranz 2023	Boucly et al 2022 + UK age
8	continuation criteria	Sotatercept only discontinued in the high-risk state, and PPA therapy initiated in high-risk state	Sotatercept discontinued in both the intermediate-high- and high-risk states
9			Sotatercept administered in high risk with 100% PPA use
10			Sotatercept administration and 100% PPA therapy in both intermediate-high and high- risk health states
11			Sotatercept administration with 50% PPA therapy in intermediate-high risk with 100% PPA therapy in high risk health state
12		24 week stopping rule for inadequate sotatercept responders	24-week stopping rule removed
13	Utilities	Adjusted baseline health state utilities per adjust-related utility ratios from general norms	Quality of life capped at general population values
14		Utilities sourced from STELLAR using risk status	WHO FC-based health state utility values from STELLAR as a proxy
15	Caregiver utilities	Excluded caregiver utilities	Inclusion of carer quality of life
16	Disutilities	Included a transplant disutility of –0.105	Removal of transplant/PAH hospitalisation disutility
17		Included an administration disutility for IV infusion only	Removal of administration disutility for IV infusion
18			Davis et al disutilities for all administration methods (inhaled, SC injection)
19	Baseline characteristics	Mean weight of STELLAR Non-US population	Mean weight of STELLAR ITT population
20	Dosing	IV PPA treatments dosing information sourced from CADTH selexipag submission	IV PPA treatment dosing information sourced from 2022 ESC/ERS guidelines
21	Combined scenario	Combining scenarios 7, 18, 20	
22		Combining scenarios 11 and 21	
23		Combining scenarios 4 and 22	
24	Time horizon	Lifetime (30 years)	10 years
25			20 years
26	Contract pricing	No contract pricing discounts	Include contract pricing discounts (ambrisentan, sildenafil citrate, tadalafil, treprostinil)

Abbreviations: CADTH: The Canadian Agency for Drugs and Technologies in Health; ERS: European Respiratory Society; ESC: European Society of Cardiology; FC: functional class; HCRU: healthcare resource use; HR: hazard ration; ICER: incremental cost-effectiveness ratio; ITC: indirect treatment comparison; ITT: intention-to-treat; LY: life-year; MAIC: matching-adjusted indirect comparison; PAH: pulmonary arterial hypertension; PPA: prostacyclin pathway analogue; SC: subcutaneous; QALY: quality-adjusted life-year; UK: United Kingdom; US: United States; WHO: World Health Organisation.

6.4. Key strengths

- The use of a Markov model structured around the ESC/ERS four risk categories reflects current clinical understanding of the PAH progression and aligns with UK treatment pathways.
- Transitions and outcomes for the first 24 weeks (decision-tree) were informed directly by STELLAR.
- Health state utilities were based on EQ-5D data collected in STELLAR, providing a relevant measure of HRQoL.

6.5. Key uncertainties

- There was no robust direct comparative evidence between sotatercept and selexipag. As a result, the relative risks of improvement and worsening used to model selexipag transitions were informed by a small, non-randomised, post hoc within-STELLAR subgroup analysis, introducing uncertainty into the comparative effectiveness input of the economic model. Scenario 3 and 4 in Table 6.3 used comparative effectiveness estimates from the Bucher ITC and MAIC, based on WHO functional class outcomes, which resulted in higher ICERs.
- Transition probabilities after week 24 were assumed to remain constant for the full-time horizon, based on changed observed between weeks 12-24 in STELLAR, implying no waning or further improvements beyond 24-weeks. The company referenced emerging data from SOTERIA extension study but only around one year of follow-up was available. Applying short-term transition patterns over a lifetime horizon introduces uncertainty in the projected long-term benefits.
- The model applied different continuation rules across arms. Sotatercept had a 24-week stopping rule and the model assumed continuation of treatment until the high-risk state; selexipag discontinued at the intermediate-high- and high-risk health states with no 24-week stopping rule. A scenario removing the stopping rule showed no material impact on the ICER (Scenario 12). Scenarios that applied uniform discontinuation criteria (Scenario 8), or that allowed sotatercept use to continue into the high-risk health state alongside PPA therapy increased the ICER (Scenario 9). A further scenario explored where sotatercept was continued into the high-risk health state, with PPA therapy introduced in the intermediate-high risk state which resulted in large increases in the ICER (Scenarios 10 and 11).
- In the base case, an administration disutility was applied only to IV PPA therapy, with no disutilities applied to other administration routes. Because escalation to IV PPA occurs more often in the selexipag arm, the assumption was a key driver of the QALY losses for the comparator. Scenario analysis showed that removing the IV disutility or applying disutilities to subcutaneous injections and inhaled administration (sourced from the same study, Davis et al 2018), increased the ICER (scenario 17 and 18).
- Mortality data associated with PAH from the STELLAR study was scarce. As a result, evidence from the literature was used. The COMPERA study provided mortality data for

patients with PAH according to ESC/ERS risk strata but was limited by small sample size and a short duration of follow-up (5-year). An alternative study[17] had a longer duration of follow-up (10-years) and a larger sample size, and when used as a basis for estimating mortality in the model resulted in a higher estimate of cost-effectiveness (Scenario 7). This was driven by higher estimated mortality in the high-risk health states which reduced the IV PCA cost offsets in the PCA arm. Other scenarios varying the extrapolation curves to the mortality data from the company's base case source also resulted in higher estimates of cost-effectiveness (Scenarios 5 and 6).

- Dosing assumptions for subsequent PPA treatments were inconsistent with UK clinical practice. The company used dosing information from a submission to Canada's Drug Agency for selexipag whereas clinical experts consulted by SMC considered the ESC/ERS guidelines to be relevant to clinical practice in Scotland. Using the ESC/ERS guidelines to determine the dose of PCA resulted in lower doses of IV epoprostenol maintenance and lowered its associated costs in the model. This led to an increase in the ICER driven by lower IV PPA cost offsets (scenario 20).
- Carer utilities were not included in the base case as per SMC guidance. A scenario analysis indicated that included carer utilities had a limited impact on the ICER (scenario 15).
- The cost of ambrisentan, sildenafil citrate, tadalafil and treprostinil in NHS practice were lower than the prices used in the economic model due to the existence of a national framework agreement for these medicines. Using the national framework contract prices had a small downward impact on the cost-effectiveness results.

*Other data were also assessed but remain confidential.**

7. Conclusion

The Committee considered the benefits of sotatercept in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as sotatercept is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the Committee was unable to accept sotatercept for use in NHSScotland.

8. Guidelines and Protocols

The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) published guidelines for the diagnosis and treatment of pulmonary hypertension in 2015, which were updated in 2022.[5]

An updated treatment algorithm was published in 2024 following the 7th World Symposium on Pulmonary Hypertension.[18]

9. Additional Information

9.1. Product availability date

02 June 2025

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 3 week cycle (£)
Sotatercept	**Single starting dose of 0.3 mg/kg, then after 3 weeks, increased to a target dose of 0.7 mg/kg every 3 weeks. Administration is via SC injection.**	**0.3mg/kg: 5,423** **0.7mg/kg: 7,230**

Costs from BNF online on 04 November 2025. Costs based on body weight of 70 kg and calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the budget impact due to commercial in confidence issues.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 12 December 2025.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.