NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Sotatercept for treating pulmonary arterial hypertension

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using sotatercept in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: August 2025

Note that this document is not NICE's final guidance on sotatercept. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using sotatercept in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 17 September 2025
- Second evaluation committee meeting: TBC
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Sotatercept, with other pulmonary arterial hypertension (PAH) treatments, should not be used to treat PAH in adults with World Health Organization functional class (WHO FC) 2 to 3, to improve exercise capacity.

1.2 This recommendation is not intended to affect treatment with sotatercept that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

Sotatercept is not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because the available evidence does not suggest that sotatercept is value for money in this population.

Why the committee made these recommendations

Usual treatment for PAH with a WHO FC of 2 to 3 is a combination of endothelin receptor antagonists and phosphodiesterase type-5 inhibitors as background treatments, plus selexipag. For PAH with a WHO FC of 3 usual treatment can also include prostaglandin I2 analogues. Sotatercept would be an alternative to selexipag.

The company asked for sotatercept to be considered only for people who have an intermediate–low-risk status to reflect the populations in the clinical trials. This does not include everyone it is licensed for.

Clinical trial evidence shows that sotatercept plus background treatments improves exercise capacity compared with placebo plus background treatments.

Sotatercept has not been directly compared in a clinical trial with selexipag, but indirect comparisons using data from 3 different studies suggest that sotatercept is likely to work better.

The cost effectiveness of sotatercept is unclear because of uncertainties with some of the assumptions in the economic model. These include:

- the long-term treatment effects when comparing sotatercept with selexipag
- how and when treatment with sotatercept or selexipag is started
- how subsequent treatments are started when PAH gets worse
- subsequent treatment effects.

Even when considering the condition's severity, and sotatercept's effect on quality and length of life, the most likely cost-effectiveness estimates are above the range that NICE considers an acceptable use of NHS resources.

So, sotatercept should not be used.

2 Information about sotatercept

Marketing authorisation indication

2.2 Sotatercept (Winrevair, Merck Sharp & Dohme) is 'indicated 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'.

Dosage in the marketing authorisation

2.3 The dosage schedule is available in the summary of product characteristics for sotatercept.

Price

2.4 £5,422.50 per 45-mg vial and £7,230.00 per 60-mg vial (not available on BNF).

2.5 The company has a commercial arrangement, which would have applied if sotatercept had been recommended.

Carbon Reduction Plan

2.6 Information on the Carbon Reduction Plan for UK carbon emissions for sotatercept will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Merck Sharp & Dohme, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Pulmonary arterial hypertension (PAH) is a rare, severe and progressive form of pulmonary hypertension caused by changes in the smaller branches of the arteries in the lungs. The condition causes the walls of the pulmonary arteries to become thick and stiff, narrowing the space for blood to pass through and increasing blood pressure. As the arteries are less able to stretch, the heart has to work harder to pump blood to the lungs. This damages the heart and makes it less efficient at pumping blood around the body and getting oxygen to the muscles.

Health-related quality of life

3.2 People with PAH experience increasingly debilitating symptoms that severely impact day-to-day living and quality of life. These include breathlessness during exercise and sometimes during rest, extreme tiredness, weakness and chest pain. Clinical and patient experts explained how, even with current treatment, the burden of symptoms is still high. The patient expert described the severe impact of PAH on their quality of life. They explained that even with current treatment they will still experience dizziness, be at risk of collapsing and have to avoid hills or stairs. They explained that living with PAH impacts mental health and self-

esteem and causes stress, frustration and anger. They noted that PAH also has an impact on carers and family members. The committee concluded that PAH is a debilitating condition that substantially affects physical, social and psychological aspects of life.

Clinical management

Current treatment of PAH

3.3 To determine prognosis and treatment, people with PAH are assessed for severity and risk status at initial diagnosis and 3 to 6 months after. Risk status can be classified by 2 different systems:

- the European Society of Cardiology/European Respiratory Society (ESC/ERS) classification or
- the World Health Organization functional class (WHO FC).

The company submission highlighted that the current treatment pathway for PAH in the UK reflects the 2022 ESC/ERS guidelines. The guidelines use risk status (predictive of risk of death in 1 year) to guide treatments decisions, with the aim of achieving and maintaining low-risk status. Risk status is assessed at diagnosis and initially classified into low, intermediate, or high-risk status. At follow up after initial treatment, people with PAH are assessed and classified into ESC/ERS risk categories: low, intermediate–low, intermediate–high, or high-risk status. People without cardiopulmonary comorbidities usually have the following treatments:

- if low risk (WHO FC 1 or 2), continue on endothelin receptor antagonist (ERA) with phosphodiesterase type 5 inhibitor (PDE5i) dual therapy
- if intermediate–low risk, continue on ERA with PDE5i dual therapy, plus selexipag as an add-on therapy
- if high or intermediate–high risk (WHO FC 3 or 4), continue on triple therapy without selexipag, that is, ERA with PDE5i and with a

prostaglandin I2 (PGI2) analogue (for example intravenous prostacyclin analogues [PCA]).

3.4 Clinical experts agreed that this treatment pathway reflects UK clinical practice and that as the disease progresses current treatment is maintained and new treatments are added on, apart from selexipag. They noted that discussing individual preferences is important in determining treatment options. A clinical expert noted that treatment often aims to maintain PAH in lower-risk states for as long as possible. Patient experts and clinical experts highlighted the unmet need for treatments for PAH, particularly in the intermediate- and high-risk groups and noted that current treatments do not always alleviate symptoms. They described the invasive nature and side-effects of having intravenous PCA, which can be frustrating and distressing. Some people need to take their PCA treatment with them everywhere, which can risk infection. Patient experts stated that they would welcome new treatments because the need is so great. Clinical and patient experts also discussed the possibility of having access to pulmonary rehabilitation and other physical therapies. The patient expert explained that pulmonary rehabilitation can provide short-term relief and is an effective treatment alongside pharmacological treatments, but it is not always available. The committee acknowledged that this treatment was positioned by the company only for PAH with an intermediate–low-risk status and so would not fully address the unmet need. The committee noted that a new treatment that could maintain low-risk status for longer could avoid more invasive treatment. It concluded that people with PAH and healthcare professionals would still welcome a new treatment option in the intermediate–low-risk group.

Positioning of sotatercept

3.5 The marketing authorisation for sotatercept includes people with a WHO FC of 2 to 3. This includes those at an ESC/ERS low-, intermediate–low- or intermediate–high-risk status. The company has positioned sotatercept for people who are intermediate–low risk at follow up. Current treatment

for this risk group is ERA with PDE5i plus selexipag as an add-on therapy (see section 3.3). So, sotatercept is positioned as an alternative treatment to selexipag. Clinical experts confirmed that people who are initially diagnosed with high-risk status and then with intermediate–low-risk status at follow up would still be considered for ERA with PDE5i plus sotatercept. The clinical experts confirmed that sotatercept is appropriate for people with an ESC/ERS intermediate–low-risk status. They also noted that in clinical practice, sotatercept could be an option for treating PAH with a broader range of ESC/ERS risk statuses. This is because WHO FC 2 and 3, as indicated in the marketing authorisation for sotatercept, includes people from low risk to intermediate–high risk. The clinical expert explained that 38% of people with PAH are intermediate–high risk and 17% are high risk. The clinical experts stated that there is an unmet need for treatments for ESC/ERS high-risk PAH, including for people who cannot have intravenous PCAs. They were concerned that sotatercept would not be used in the intermediate–high-risk groups if recommended. The company stated that the marketing authorisation may be broadened in the future to cover WHO FC 4. The company explained that their positioning of sotatercept for ESC/ERS intermediate–low-risk PAH is based on the current marketing authorisation and available study data. The committee noted that the primary study, STELLAR (see section 3.5), included people with a WHO FC 2 and 3 and so would include some people with intermediate–high-risk status. The committee understood that the company's positioning of sotatercept for ESC/ERS intermediate–low-risk PAH was narrower than its marketing authorisation. It noted that this treatment could benefit other risk groups within the marketing authorisation. The committee also understood that there are other published studies and potentially data from the STELLAR trial that may allow for this analysis.

Clinical effectiveness

Clinical effectiveness evidence

3.6 STELLAR (n=323) is a multicentre, double-blind, phase 3 randomised placebo-controlled trial in adults with WHO functional class 2 or 3 PAH. People had sotatercept (n=163) or placebo (n=160) as an injection every 21 days in addition to background mono, dual or triple therapy. The primary endpoint was the change from baseline at week 24 in the 6-minute walk distance (6MWD). At 24 weeks the observed mean change from baseline was 40.3 metres with a standard deviation of 64.18 in the sotatercept group. This was higher than the placebo group at the same point (-0.6 metres with a standard deviation of 69.54). This trend continued up to week 84. The median treatment difference in 6MWD between the sotatercept and placebo groups was 40.4 metres (95% confidence interval 27.28 to 53.53, $p<0.001$). Clinical experts noted that the minimal clinically important difference in 6MWD was defined at 33 metres. At week 24, a significantly greater proportion of people had an improvement in 6MWD of at least 30 metres in the sotatercept arm than the placebo arm (54% compared with 22%).

SOTERIA (n=426) is a long-term, open-label extension study of adults with PAH who have completed prior sotatercept trials (SPECTRA, PULSAR, ZENITH, HYPERION, STELLAR). People could enter SOTERIA if they had a clinical worsening event or completed the 24-week treatment period in the STELLAR trial. SOTERIA reports on the long-term safety data of sotatercept but the results from this study are not included in the modelling.

Indirect treatment comparisons

3.7 The company did an indirect treatment comparison (ITC) comparing sotatercept (data from STELLAR) with selexipag (data from GRIPHON and TRACE). GRIPHON (phase 3) and TRACE (phase 4) are studies comparing selexipag plus background therapy with placebo plus background therapy. The results of the ITC are confidential and cannot be reported here. The EAG highlighted that STELLAR had a longer duration from diagnosis to randomisation than GRIPHON (so the STALLAR

population was more stable and responded better) and its participants had more background therapy. The EAG also highlighted that there was a difference in the risk stratification used. STELLAR used ESC/ERS risk stratification guidelines whereas GRIPHON used WHO FC risk stratification, which is more common in trials but is also less sensitive. The company also attempted to do other ITCs, including one that compared sotatercept with intravenous PCA. But, the ITC was not feasible because of a lack of common comparator. The company explained that this is one of the considerations in positioning sotatercept for intermediate–low risk only (see section 3.4).

Post-hoc analysis using STELLAR data

3.8 The company did a post-hoc within-trial analysis of STELLAR to assess the outcome of change from baseline in ESC/ERS risk status at week 24. This analysis included people having the following treatments:

- PDE5i with ERA in the sotatercept arm
- PDE5i with ERA plus selexipag in the placebo arm.

The results showed the likelihood of improving or worsening risk status for people who had sotatercept compared with people who had selexipag as part of their background therapy. The results of the within-trial analysis are confidential and cannot be reported here. The EAG expressed that this post-hoc analysis was not predefined and it considered it to be inappropriate. The EAG explained that a direct comparison was not possible between these 2 groups and that the results from this post-hoc analysis could be biased in favour of sotatercept because:

- The placebo arm was already having PDE5i with ERAs plus selexipag as background therapy before the beginning of the trial. So any treatment effect of selexipag that happened from the start of treatment to randomisation is unobservable.

- Randomisation is broken because the analysis compares double background therapy with triple background therapy at baseline.
- People who are having triple combination therapy are having more intensive treatment and so are likely to have a worse prognosis.

The company confirmed that at the start of the analysis people may have been having background therapy (including selexipag) for between 90 days and 8 years. The clinical and patient experts agreed that at 90 days people on background therapy are likely to be stable. The clinical expert stated that a large proportion of background treatment (this includes PDE5i with ERA plus selexipag) benefit is seen at initiation or soon after, and they would expect a therapeutic effect by 90 days. This is why assessments of clinical effectiveness are done around this time in clinical practice. The company stated that the 2 populations being compared were well balanced. The committee noted some differences between the sotatercept and the placebo arms, such as age, time from diagnosis and baseline risk status and considered this to be a naive comparison. The committee concluded that because of the potential bias in the company's within-trial post-hoc analysis, the EAG's ITC approach should be used in decision making (see section 3.9). The committee also noted the potential benefit of further analysis, such as propensity score matching (see NICE technical support document 17). This could help to account for the differences in subgroups' baseline characteristics and with understanding how differences may impact the results. This may help to determine to what extent the within-trial analysis data can be used, if at all. But, the committee acknowledged that this would not resolve the differences between when treatment began in both groups and how this impacts the observed treatment effect for selexipag.

Economic model

Modelling approach

3.9 The company presented a Markov cohort model based on previous models in PAH. To reflect changes in clinical management (see section 3.3) the company updated the model structure using the ESC/ERS low-risk states rather than WHO FC states. The risk states reflect increasing risks of mortality and have been incorporated in the model using hazard ratios relative to the low-risk state. The EAG acknowledged that the model captures the progression of current management of PAH. But, it noted that the current commissioning guidelines for comparator treatments still refer to WHO FC rather than ESC/ERS risk strata. The EAG raised concerns around differences in how sotatercept and selexipag treatment is started (see section 3.12). The EAG also disagreed with the company's assumption of not allowing for clinical improvement after starting PGI2 in the intermediate–high and high-risk states of the model (see section 3.11). The company modelled mortality using increasing ESC/ERS risk status based on Kaplan–Meier survival data from Rosenkranz et al. (2023), with survival data from the COMPERA PAH registry. The company used a dependent parametric regression model (Gompertz) with non-low-risk states fitted as covariates fitted to the Kaplan–Meier survival data. This was selected based on expert opinion. The company and the EAG acknowledged that the approach to modelling mortality was highly uncertain. The EAG notes that how overall survival is modelled has a big impact on projected life years. The committee acknowledged that any further analysis should include different modelling approaches within the sensitivity analysis. It concluded that there are concerns with the company's model (see section 3.10, section 3.11 and section 3.13), and with the uncertainty in overall survival extrapolation, that will need to be addressed.

Short-term transition probabilities for selexipag

3.10 To inform the selexipag transition probabilities in the model, the company used the relative risk of ESC/ERS risk status improvement or deterioration from the STELLAR trial analysis (see section 3.7). It applied these to the estimated transition probabilities for sotatercept in the model. The

company explained that it used this approach because an ITC to compare change in ESC/ERS risk status from baseline was not possible because this outcome was not included in the ITC data. The EAG explained that the company's method would introduce bias towards sotatercept (see section 3.8). The EAG preferred using the ITC with GRIPHON and TRACE. This was because, although GRIPHON included WHO FC states (see section 3.6), it would provide less biased estimates of the relative risk for improvement or deterioration. The committee acknowledged the different risk stratification systems used between STELLAR and GRIPHON and also that the WHO FC stratification is less sensitive than ESC/ERS. The committee suggested that a matching-adjusted indirect comparison could be used in this ITC. This could address the differences in baseline characteristics between STELLAR and GRIPHON and TRACE and would make the analysis more robust. The committee concluded that on balance, both methods had limitations and were uncertain (see section 3.7), but it preferred the EAG's approach. This was because the short-term transition probabilities for selexipag were informed by data where the largest treatment effects (such as 6WMD) can be observed in both arms and randomisation was preserved and so may be less biased.

Long-term transition probabilities

3.11 The short-term relative risks (see section 3.9) are used to derive long-term transition probabilities for sotatercept and selexipag over the entire time horizon of the model. The company stated that the reapplication of the short-term relative risks over long-term cycles was appropriate. This was because the results from SOTERIA showed no treatment waning effect over time and so it would be possible to assume a constant treatment effect for sotatercept. The EAG stated that this method lacked clinical validity because it meant that almost no one in the selexipag arm remained in lower-risk states after a certain period of time. The EAG suggested that the ITC with GRIPHON and TRACE would provide less biased results of the relative risks for risk status improvement or deterioration for selexipag (see section 3.9). The EAG also highlighted

that even with the ITC relative risks, the reapplication of the same transition probabilities may overestimate risk status deterioration in selexipag. So, the EAG suggested reducing the magnitude of these effects when applying them to long-term transition probabilities. The EAG did multiple scenario analyses varying the relative risk reduction of treatment effects from 100% to 25%. The EAG presented modelled projections to represent the percentage survival and progression for each scenario analysis. The clinical expert stated that the projection using the ITC with GRIPHON and TRACE may be plausible (this information is considered commercial in confidence) and that the within-trial analysis projects where less plausible. But they agreed that the EAG mid scenario projections, which assume a 50% reduction in the relative risk of risk status deterioration, are the most plausible. The committee concluded that it would be reasonable to use the EAG mid scenario percentage of relative risk reduction to the treatment effects. But it also discussed the need for alternative data sets to inform and validate the relative risk reduction.

No clinical improvement after PGI2 initiation

3.12 In the model, people move to the intermediate–high and high-risk states on disease progression. On entering these states, intravenous PCA is started as a subsequent treatment. The possibility for improvements in risk status (backwards transitions) are switched off or not included in the model for subsequent intravenous PCA. The company stated that clinical improvement on intravenous PCA was not included in the selexipag arm because the evidence for its efficacy in the intermediate–low-risk group was uncertain. The costs of intravenous PCA and a utility decrement for administration of intravenous PCAs are included in the model. But the EAG noted that it was possible for clinical improvement in the sotatercept arm after starting PGI2. At clarification, the EAG queried the difference in assumptions about improvement on intravenous PCA. To resolve this, the company removed the ability to improve risk status in the sotatercept arm. The company stated that they could not add this function in the selexipag

arm because of time constraints. The patient experts had a mixed experience with intravenous PCAs and both discussed the high treatment burden. One patient expert explained that they have had a maintained benefit over time when having treatment with intravenous PCAs. The clinical expert agreed that clinical improvement can be seen after starting intravenous PCAs. But, they stated that the main benefit of intravenous PCAs is stability in the intermediate–high or high-risk states. This contributes towards increasing exercise capacity, improving 6MWD, and reducing mortality. The committee concluded that including the intravenous PCA utility decrement and costs but not the utility increments from intravenous PCA treatment is inappropriate and does not reflect clinical and patient experiences. So, the model structure should reflect improvements in risk status after starting intravenous PCA.

Initiation of PGI2 analogues in the sotatercept arm

3.13 In the company model, people who had progressed to an intermediate–high-risk state on sotatercept remained on sotatercept but did not start PGI2 analogues. The company stated that this reflected clinical practice in the NHS for people who had progressed to intermediate–high-risk. In the model, The EAG preferred to add PGI2 analogues to 39.9% of the sotatercept arm on progression to the intermediate–high-risk state. This aligns with the proportion that start PGI2 analogues on progression to an intermediate–high-risk state in STELLAR. This was used to inform the transition probabilities from the intermediate–high-risk state and aligns better with clinical expert opinion provided to the EAG.

People who had progressed to a high-risk state on sotatercept stopped sotatercept and started PGI2 analogue treatment. The company and the EAG base cases assumed that for the high-risk group sotatercept is stopped. This is because there is no data to account for increased efficacy of sotatercept plus intravenous PCAs (a PGI2 analogue) compared with background treatment for the high-risk group in the selexipag arm. The clinical experts confirmed it is likely that intravenous PCAs would be

added to sotatercept without stopping sotatercept treatment. For progression to the intermediate–high-risk state, the committee concluded that the EAG's approach was the most appropriate because it was supported by clinical trial evidence and expert opinion. For progression to the high-risk state, the committee acknowledged that the EAG and company base cases both included the assumption of stopping sotatercept due to lack of data. It highlighted that if usual practice is to continue sotatercept with intravenous PCAs, significant costs of sotatercept may not be captured in the model. The committee requests further scenario analyses including exploration of other data sources around sotatercept with PCA analogues. It discussed that these analyses could be potentially informed by ZENITH data.

Proportion of PGI2 analogues

3.14 In the company's base case, 100% of people had PGI2 analogues in both arms in the model when they progressed to intermediate–high and higher risk states. The company stated that this was in line with the World Symposia guidelines on pulmonary hypertension. Clinical expert advice to the EAG suggested that intravenous PCA (a PGI2 analogue) would not be suitable for all people and not all people offered would accept it. The patient experts agreed with this. The EAG also suggested that in the intermediate–high to high-risk states it would be reasonable to assume 85% would have PGI2 analogues but it could be lower in real-world practice. The EAG assumed that 85% of people will have PGI2 analogues on progression to the intermediate–high-risk and high-risk state in the selexipag arm and the high-risk state in the sotatercept arm. For those that progress to intermediate–high in the sotatercept arm, they assumed that 39.9% have PGI2 analogues, which was informed by the figures in the STELLAR trial. The remainder are assumed to remain on their current treatment regimen. This estimate considered both intravenous and inhaled preparations of PCA. The clinical expert cited the REVEAL registry showing that 50% of high-risk people with a WHO FC of 4 had intravenous PCAs. The EAG's approach, in which less than 100% of

people who progressed received PGI2 analogues, was supported by the estimates provided by clinical and patient experts during the meeting. So, the committee concluded that the EAG's approach was the most appropriate and should be used in the model.

Weight-based dosing of intravenous PCA

3.15 The company based the dosing of intravenous PCA preparations on a Canadian Drug Agency appraisal of selexipag. The company used a target dose of epoprostenol at 50 ng/kg/minute and at 30 ng/kg/minute for treprostinil. Clinical expert opinion to the EAG suggested these doses are higher than the doses used routinely in NHS practice. This suggests over costing of epoprostenol, the most frequently used intravenous PCA preparation in the NHS, and potential bias in favour of sotatercept. The EAG also highlighted that the company's approach excluded US participants for weight-based dosing but has included all other countries, including those with a lower average weight than the UK. At clarification, the company provided some scenario analysis with different average weights. This demonstrated a small increase in the incremental cost-effectiveness ratio (ICER). The EAG preferred to apply dosing for PGI2 analogues as per the ESC/ERS guidelines. That is, epoprostenol 23 ng/kg/minute (midpoint of 16 to 30 ng/kg/minute), treprostinil 42.5 ng/kg/minute (midpoint of 25 to 60 ng/kg/minute). The clinical experts confirmed that dosing based on ESC/ERS guidelines is appropriate. The committee acknowledged that the company has accounted for wastage in its modelling. The committee concluded that the EAG's approach is in line with clinical practice and should be used in the model.

Utility in the model

3.16 The company included 3 additional utility increments and decrements in the model:

- a decrement for intravenous PCA administration
- a decrement for hospitalisation and

- an increment for carers of people in less-severe risk states instead of a decrement for carers of people in high-risk states.

The carer utility increment was accepted and included in the EAG base case. The EAG stated that a key concern of including a utility decrement for intravenous PCA administration was that no clinical improvement was included for intravenous PCA analogues in the model. The company noted that they did not use EQ-5D data from STELLAR because there were too few observations in some of the risk strata at 24 weeks (see section 3.11). For the decrement on hospitalisation, the company used a published utility decrement for hospitalisation within 30 days (McMurray et al. 2018). The EAG stated that according to the literature, the decrement applied might be an overestimation and partially double count the impact of hospitalisation. It may also have not adjusted for cycle length. The EAG explained that the McMurray et al. study included a reduced utility decrement for hospitalisation within 90 days and therefore combined both values in their base case.

The committee concluded that:

- EQ-5D data from STELLAR should be used to provide insight into overall improvement intravenous PCA is started
- the utility decrement associated with hospitalisation should be reduced from 0.105 to 0.071, applied for the duration of the cycle in which events occur (to align more closely with utility for hospitalisation between 0 and 90 days) and if no possibility of clinical improvement after starting PGI2 is added
- intravenous PCA administration disutility should be removed (to compensate for the lack of clinical benefit included in the model for these treatments).

The committee recalled the impact that PAH had on carers and family

members (see section 3.2) and concluded that it was appropriate to include an increment for carers of people in less-severe risk states.

Preferred assumptions

3.17 After comparing both the company and the EAG base cases, the committee preferred the following assumptions:

- a model structure that can reflect improvements in risk status after starting PCA (see section 3.8)
- short-term transition probabilities for selexipag informed by application of WHO FC relative risks derived from the ITC with GRIPHON and TRACE (see section 3.9)
- long-term transition probabilities for selexipag derived by applying half of the relative risk reduction of disease progression observed for sotatercept versus selexipag at 24 weeks, based on the ITC with GRIPHON and TRACE (see section 3.10)
- removal of the intravenous PCA administration disutility if there is no possibility of clinical improvement after starting PGI2 (see section 3.11)
- a utility decrement associated with hospitalisation of 0.071, applied for the duration of the cycle in which events occur (see section 3.15)
- PGI2 analogues added to sotatercept for 39.9% of people on progression to the intermediate–high-risk state on sotatercept (see section 3.12)
- 85% (rather than 100%) have PGI2 analogues following progression to the intermediate–high-risk or high-risk state on selexipag (or to the high-risk state on sotatercept [see section 3.13])
- dosing assumed to be 23 ng/kg/minute for epoprostenol and 42.5 ng/kg/minute for treprostinil, based on target maintenance doses in ESC/ERS guidelines (see section 3.14)
- hospitalisation quality-adjusted life year (QALY) loss calculations adjusted to the 12-week cycle length of the model (to correct a minor calculation inconsistency).

Severity

3.18 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. In the company submission, the EAG agreed that the case was met for application of a severity weighting of 1.2 on QALY gains. This was based on the absolute shortfall versus the expected QALYs of the age and sex matched general population. The values for the QALY shortfall are confidential. The committee noted that in some scenarios presented, a 1.2 multiplier may not hold. These scenarios included aligning population age and sex with those reported in the UK National Audit of Pulmonary Hypertension (NAPH) and different methods of modelling mortality. The EAG explained that the company's approach to modelling mortality was reasonable but that the UK NAPH may be more representative of the population seen in clinical practice. The committee agreed that aligning to the baseline characteristics of UK NAPH would be more relevant to the population of people with PAH. The committee noted that more information would be needed to make a decision on the appropriate severity modifier in further analysis. The committee concluded that the severity will be reassessed following the updated model structure and alignment with the UK NAPH population.

Cost-effectiveness estimates

Acceptable ICER

3.19 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain

about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically with:

- The transition probabilities used to determine relative risk of improvement or deterioration in the model. While the committee preferred the EAG approach, there was still a concern that both approaches had areas of uncertainty. Specifically, the sensitivity of WHO FC compared with the ESC/ERS risk stratification.
- The long-term efficacy of sotatercept compared with selexipag.
- The assumption that there is no clinical improvement after starting PGI2 analogues, which does not reflect clinical practice.
- The timing and approach to starting PGI2 in the sotatercept arm of the model, which is inconsistent with clinical expert feedback received by the EAG.
- The proportion of people having PGI2 analogues.

Further analysis is needed from the company. So, the committee was not able to decide on an acceptable ICER.

Other considerations

Equality

3.20 The committee considered that some older people and people with PAH who are menstruating may not be considered for sotatercept because of an increased risk of bleeding and associated complications. The committee also acknowledged that this treatment requires additional specialist centre visits. The clinical expert highlighted that because of this sotatercept accessibility could be affected by ability to travel, symptom burden, financial burden and mobility. The committee discussed that people with some disabilities may require additional at-home support to administer the treatment. Characteristics such as age, sex and disability are protected characteristics under the Equality Act 2010. But because a recommendation would not restrict access to treatment for some people

over others, the committee agreed these were not potential equalities issues.

Uncaptured benefit

3.21 The committee considered whether there were any uncaptured benefits of sotatercept. It did not identify additional benefits of sotatercept not captured in the economic modelling. So the committee concluded that all additional benefits of sotatercept had already been taken into account.

Conclusion

3.22 The committee recognised the unmet need for people with PAH who may have a high symptom burden even with current treatments. The committee acknowledged that sotatercept's marketing authorisation includes people considered to have low-, intermediate–low- to intermediate–high-risk PAH. It noted that while the company positioned it for people with intermediate–low-risk status, there is evidence published since the company submission that suggests this could benefit people in intermediate–high- or high-risk states. The committee expressed that this option should be explored before the next committee meeting. The committee discussed the issues raised by the EAG. While it agreed with the majority of the EAGs preferred assumptions there were still uncertainties that may be addressed by further analysis.

The committee concluded that it was not able to decide on an acceptable ICER at this stage. Further analysis is needed for:

- comparing sotatercept with PCA analogues in the intermediate–high- and high-risk populations, using published data discussed by clinical experts in the meeting
- adapting the structure of the model to allow for clinical improvement after starting PCA
- providing a further analysis such as propensity scoring (NICE technical support document 17) to account for the difference between the subpopulations compared in the post-hoc STELLAR trial analysis

- using alternative data sets to validate the relative risk reduction from the ITC with GRIPHON and TRACE that was used in the model
- updated analyses using the committee's preferred assumptions with appropriate scenario analysis, including alignment to the UK NAPH, starting PCA analogues with sotatercept and including different modelling approaches for overall survival within the sensitivity analysis.

The committee considered the uncertainty that could be addressed with further analysis and that it had not been able to decide on an acceptable ICER based on the current analyses presented. So, it concluded that sotatercept should not be used to treat PAH in adults with World Health Organization functional class (WHO FC) 2 to 3, to improve exercise capacity.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

James Fotheringham

Chair, technology appraisal committee A

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

Alice Bell
Technical lead

Caron Jones
Technical adviser

Jeremy Powell
Project manager

Emily Crowe
Associate director

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