National Institute for Health and Care Excellence

Health Technology Evaluation

Sotatercept for treating pulmonary arterial hypertension ID6163
Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	MSD (company)	MSD agrees that an evaluation of this topic via the single technology appraisal route is appropriate.	Thank you for your comment.
	NHS England	NICE intends to evaluate this technology through its Single Technology Appraisal process. This is appropriate but note that there is an established treatment pathway commissioned by NHS England that includes high-cost medicines, none of which have been subject to NICE appraisal. This means that sotatercept will be the first therapy for pulmonary arterial hypertension (PAH) to go through this route.	Thank you for your comment.
Wording	MSD (company)	The wording of the remit is appropriate.	Thank you for your comment.

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	NHS England	NICE describes the remit as: *To appraise the clinical and cost effectiveness of sotatercept within its marketing authorisation for treating pulmonary arterial hypertension.* This wording seems appropriate as it reflects the expected marketing authorisation. Specification of use for patients in risk groups as defined by ESC/ERS guidelines would be helpful in addition to WHO FC eg some patients in WHO FC II may have adverse prognostic features (particularly young patients who have most to gain from therapy) if access is limited to patients with WHO FC III and FC IV.	Thank you for your comment. Potential subgroups will be considered in the technology appraisal for sotatercept. No change to scope required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	MSD (company)	The draft background section references data from the 2015 National Audit of Pulmonary Hypertension, however more up-to-date data from the 13th annual report of the National Audit of Pulmonary Hypertension (2021-2022) are now available. These data demonstrate that there are currently 4,269 patients living with PAH in the UK, with 568 new diagnoses each year, equating to a prevalence and incidence of 64 and 8.5 per 1,000,000 respectively. MSD would suggest that the following surgical interventions are removed from the list of treatments for PAH, as they are rarely used and are not indicated in the current ERS/ESC 2022 guidelines: pulmonary endarterectomy, balloon pulmonary angioplasty. We also suggest changing “Arterial septostomy” to “Atrial septostomy”.	Thank you for your comments. The background section of the scope has been updated to reflect these more recent numbers. The surgical interventions have been amended as suggested. “Conventional treatments” has been changed to “supportive treatments”, with a comment to underline

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		MSD also suggest changing the wording in the background section from "conventional treatments" to "supportive treatments" as those listed are very infrequently used in PAH care and predominantly prescribed for symptom management only.	that these are predominantly for symptom management.
	Janssen (comparator company)	Re statement "1 Data from a 2015 National Audit of Pulmonary Hypertension estimated that there were 2,657 people being treated for PAH within an active specialist centre in England.2" We note that more recent audit information is available, and maybe more relevant. Re the surgical interventions described: Pulmonary endarterectomy and balloon pulmonary angioplasty are surgical interventions for Chronic Thromboembolic Pulmonary Hypertension (CTEPH), but not Pulmonary Arterial Hypertension (PAH) as indicated here.	Thank you for your comments. The background section of the scope has been updated to reflect these more recent numbers. The surgical interventions have been amended as suggested.
	NHS England	1. Background information includes mention of CTEPH and pulmonary endarterectomy as a treatment option. Note that pulmonary endarterectomy is only indicated in CTEPH, not PAH. As Sotatercept is not seeking a license for CTEPH, suggest removal of all references to CTEPH and its treatment. There are no data on this therapy in CTEPH and it would not be our intention to consider using sotatercept in patients with CTEPH based on current evidence. 2. Background information includes anticoagulation/warfarin as a treatment option. Note that this is no longer used in PAH. 3. The section on **Related NICE recommendations** includes 3 documents. None of these is relevant to PAH and they should be removed. Two of the guidelines relate to systemic hypertension, which	Thank you for your comment. The surgical interventions have been amended as suggested. Reference to warfarin has been removed from the scope. The related NICE recommendations section has been amended as suggested.

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		is different to pulmonary hypertension. The 3rd document relates to CTEPH which is not expected to be an indication for sotatercept. 4. Note that a treatment algorithm and updates to the national policy for targeted therapies have been proposed. Practice for the treatment of PAH has evolved since the national policy was first published and is more aligned to the 2022 ESC/ERS Guideline approach. Combination oral is now accepted as standard of care for PAH.	The background section has been updated to include reference to the anticipated treatment algorithm and update to national policy for targeted therapies, and that dual oral therapy is now standard of care for PAH.
Population	MSD (company)	The currently anticipated marketing authorisation wording for sotatercept in this indication is: [redacted] It would therefore be appropriate to include in the definition of the population that patients should be [redacted]. In line with the population in the pivotal STELLAR trial, the anticipated population includes patients on background dual or triple therapy. Patients on background monotherapy are not expected to receive treatment with sotatercept in the UK.	Thank you for your comment. The NICE remit and population in the scope is kept broad, in line with the clinical trial, until the marketing authorisation is granted. The background section has been amended to indicate that PAH is a condition that will progress regardless of early detection and treatment.

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		It should also be noted in the background section that even with early detection of PAH and current treatments for it, the disease still progresses and the unmet need remains significant.	
	NHS England	See most recent national audit National Audit of Pulmonary Hypertension, 13th Annual Report - NHS Digital You may wish to exclude patients with forms of PAH specifically excluded by the trial protocol.	Thank you for your comment. The NICE population in the scope is kept broad, in line with the clinical trial, until the marketing authorisation is granted. No change to scope required.
Subgroups	MSD (company)	Based on the treatment pathway of PAH in the UK and the associated commissioning policies for treatments, it may be appropriate to consider subgroups based on background therapy regimen.	Thank you for your comment. The scope has been amended to include the possibility of subgroup analysis based on background therapy regimen if there is suitable data to enable this analysis.
	NHS England	No subgroups described in the scope. Data on sotatercept includes patients with various forms of PAH. The current data supports the use of this therapy in PAH but not CTEPH. Based on current evidence, service leads would consider sotatercept for newly diagnosed patients at the first follow-up assessment at 3- 4 months (patients will be on combination oral therapy (PDE5i and ERA or parenteral prostanoid	Thank you for your comment. The scope has been amended to include the possibility of subgroup analysis based on background therapy regimen if there

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		usually in combination) where it would be used as an additional therapy for patients who had not met their treatment goal. For prevalent patients with PAH the majority who are likely to be established on combination therapy (PDE5i + ERA , PDE5i + ERA + selexipag, Riociguat ERA or parenteral prostanoid in combination with ERA/PDE5i/riociguat) where it may be considered as an additional therapy. Depending on treatment response it may be possible to consider reviewing other PAH medications. Like all other targeted therapies, we anticipate sotatercept will be largely supplied to patients at home through homecare delivery (requiring cold storage) and these requirements have already been raised as part of the national homecare framework for PH led by CMU.	is suitable data to enable this analysis.
Comparators	MSD (company)	Based on the currently anticipated marketing authorisation wording for sotatercept and patient population relevant to this appraisal as described above, the following comparators listed in the draft scope are not relevant/appropriate: • Anticoagulant medication: warfarin • Diuretic medication: furosemide, bumetanide, and metolazone • Calcium channel blockers: nifedipine, diltiazem, nicardipine, and amlodipine The relevant comparators are the standard of care with dual- and triple-therapy used in UK clinical practice as specified in the relevant NHS England commissioning policies below: • Targeted Therapies for use in Pulmonary Hypertension in Adults, July 2015, A11/P/c. • Riociguat for pulmonary arterial hypertension, February 2017, 16055/P. • Selexipag for treating pulmonary arterial hypertension (adults), December 2018, 170104P.	Thank you for your comment. The comparators in the scope have been updated to reflect that these are not considered to be relevant comparators for sotatercept.

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	Janssen (comparator company)	- Iloprost and treprostinil are additional prostaglandins to consider	Thank you for your comment. The comparators section of the scope has been updated to include prostanoids such as intravenous/inhaled iloprost and trepostinil.
	NHS England	Comparators are listed as • ~~anticoagulant medication: warfarin~~ • diuretic medication: furosemide, bumetanide, and metolazone • calcium channel blockers: nifedipine, diltiazem, nicardipine, and amlodipine • endothelin receptor antagonists: ambrisentan, bosentan, and macitentan • phosphodiesterase 5 inhibitors: sildenafil and tadalafil • prostaglandins: epoprostenol and selexipag • soluble guanylate cyclase stimulators: riociguat Key comparators for sotatercept will be ERAs (ambrisentan at al), prostaglandins, and sGCS (riociguat)	Thank you for your comment. The comparators in the scope have been updated to reflect that warfarin is not considered to be a relevant comparator for sotatercept. The scoping workshop concluded that diuretic medication and calcium channel blockers were also not considered to be relevant comparators, and so these have also been excluded from the scope.

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Outcomes	MSD (company)	MSD suggests the following outcomes should be used for assessment of therapeutic efficacy, as they are both recognised metrics of disease progression and are frequently reported trial metrics (including for the STELLAR study): • Exercise capacity, as measured by 6-minute walk distance • NT-proBNP • WHO FC maintenance or improvement • Multi-component improvement (a combined metric of composed of the three measures listed above)) • Time to death or clinical worsening event • Pulmonary vascular resistance • European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk status • Delay in subsequent treatments • Patient reported outcomes • Adverse events	Thank you for your comment. The outcomes section of the NICE scope aims to broadly reflect the most important outcomes that should be considered, but does not necessarily include every outcome used in the relevant trial(s) or proscriptively define specific measures that must be used. No change to scope required.
	NHS England	Outcomes are listed as: • time to first confirmed morbidity or mortality event • overall survival • transplant-free survival • exercise capacity • haemodynamic assessment (e.g. cardiac index, cardiac output, right atrial pressure, pulmonary arterial pressure and pulmonary vascular resistance) • adverse effects of treatment • health-related quality of life.	Thank you for your comment. No change to scope required.

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		No other outcomes suggested.	
Equality	MSD (company)	The draft remit and scope do not need changes in order to meet NICE's commitment to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.	Thank you for your comment. No change to scope required.
	Janssen (comparator company)	- Disabled patients may have difficulties attending in hospital appointments necessary for the initiation of the therapy. Those with visual impairments or challenges with manual dexterity may have challenges self-administering SC injections. - Older patients may be less considered for this therapy due to increase risk of and consequence from bleeding. This may be a consideration in menstruating women.	Thank you for your comment. Equalities issues will be considered as part of the evaluation. No change to scope required.
	NHS England	Note patients/carers will need to administer the drug as a subcutaneous injection so how this would be used in patients unable to administer the injection themselves due to diasabilities should be considered.	Thank you for your comment. Equalities issues will be considered as part of the evaluation. No change to scope required.
Questions for consultation	MSD (company)	**Question:** Where do you consider sotatercept will fit into the existing care pathway for PAH? **Response:** The appropriate place of sotatercept in the care pathway of PAH is as described in the currently anticipated marketing authorisation wording for sotatercept which is [redacted]	Thank you for your comments.

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		[redacted].	
		Sotatercept is to be used on top of dual therapy or later.	
		Question: Have all the relevant comparators been included in the scope?	
		Response: The relevant comparators are as described in the comments above.	
		Question: What is standard of care for PAH?	
		Response: The standard of care for PAH is defined by the ERS/ESC 2022 guidelines. This outlines a progressive escalation of medical therapy according to the risk of mortality of the patient at assessment.	
		Risk of mortality is defined by a 3-strata or 4-strata model which utilises the metrics of disease progression as outlined above.	
		Question: What is the accepted definition of background therapy in the context of PAH?	
		Response: MSD considers background therapy to be a targeted PAH therapy (as defined above) which has been prescribed to a patient as standard of care.	
		Question: Is the World Health Organization (WHO) Functional Class measure used to determine which treatments people with PAH would be offered?	

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		Response: Yes. In NHS England these are described in the commissioning guidelines relevant to PAH listed below: • Targeted Therapies for Pulmonary Hypertension Functional Class II, April 2013, NHSCB/A11/P/a. • Targeted Therapies for use in Pulmonary Hypertension in Adults, July 2015, A11/P/c. • Riociguat for pulmonary arterial hypertension, February 2017, 16055/P. • Selexipag for treating pulmonary arterial hypertension (adults), December 2018, 170104P. It is important to note that in contrast to these commissioning policies mentioned above the ERS/ESC treatment guidelines do not restrict combination therapy based on WHO FC. **Question:** In clinical trials of sotatercept, participants were classified according to functional class, whether or not symptomatic, time since diagnosis and risk score. In which populations would sotatercept be used? **Response:** The specific populations in which sotatercept would be used are described previously in the comments on the draft population and the comments on the draft comparators. In summary, sotatercept would be indicated for patients in WHO FC II or III on stable background therapy consisting of dual or triple therapy who are not at goal. With regard to the clinical trials of sotatercept, it should be noted that: • WHO FC reflects symptom burden and sotatercept was studied in WHO FC II/III patients i.e. symptomatic patients. • Time since diagnosis was not used as a stratification factor in the clinical trials. There is a wide range in time to diagnosis in the patients included in the trials which reflects what is observed in clinical practice. • Risk score was not used as a stratification factor in the clinical trials. There is a wide range in risk score in the patients included in the trials.	

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		Question: Would sotatercept be a candidate for managed access? **Response:** [redacted] **Question:** Do you consider that the use of sotatercept can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? **Response:** Long term data from the STELLAR study shows clinical improvements are maintained. Treatment with sotatercept may also allow patients to come off intensive IV therapy, this will substantially reduce contact with HCPs and hospitals, along with invasive investigations/complications associated with IV administration. Overall, this has a substantial impact to patients, despite not being captured in QALY. Furthermore, treatment with sotatercept is once every 3 weeks by self-administered subcutaneous injection and there is one dose titration. This has a potentially substantially lower healthcare resource utilisation burden compared to titration of other PAH targeted therapies. There are also likely to be societal benefits and alleviation of caregiver burden associated with treatment with sotatercept. These benefits would not be captured in the QALY calculation. **Question:** Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.	

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		Response: Data to support the above will be available from the STELLAR trial results and the approved sotatercept dosing schedule, as well as its associated long-term follow-up SOTERIA trial. Societal benefits and benefits associated with the alleviation of caregiver burden may be captured from other studies that examine these topics. **Question:** NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. **Response:** No changes are necessary.	
	Janssen (comparator company)	Where do you consider sotatercept will fit into the existing care pathway for PAH? - Most participants included in trial were prevalent with long disease duration and significant proportion on triple therapy. It is not known what the impact of therapy is for those that are newly diagnosed or within one year of therapies. Therefore, we anticipate that this would be an add-on treatment to triple therapy. The majority of trial participants are of the iPAH aetiology. What is standard of care for PAH? - Patients are placed on therapies according to the ERS/ESC guidelines stratification table (Fig 9). Patients are stratified at assessment being with or without comorbidities. Those with co-morbidities are recommended to be treated with monotherapy with a PDE5i or ERA. Those that are assessed to be without co-morbidities	Thank you for your comments.

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		are further stratified as low or intermediate risk (treated with dual PDE5i and ERA therapy) or high risk (triple therapy with ERA, PDE5i and iv/sc PCA). These patients should be reassessed at 3-6 months or in the case of clinical worsening against 4 strata. If assessed to be low risk they continue the current therapy regime, if intermediate-low they would add a prostacyclin receptor analogue or switch PDE5i to sGCs or if intermediate-high or high, they would add a iv/sc PCA and/or could be evaluated for lung transplantation. - Most centres in the UK do follow this guidance, although there is some variability. What is the accepted definition of background therapy in the context of PAH? - Supportive therapy including diuretics, oxygen, anticoagulants and digoxin. Patient may also be on a number of therapies for comorbidities. - Background therapy is considered to include a number of potential therapies and combinations that a patient may be prescribed for PAH in line with their risk stratification and clinician preference and could range from mono therapy to triple therapy, with the investigational product being an 'add-on' to this SOC. Is the World Health Organization (WHO) Functional Class measure used to determine which treatments people with PAH would be offered? - FC is a subjective measure that forms part of the panel of assessments and investigations that contribute to risk stratification as outlined in the ERS/ ESC guidelines in both initial 3 strata assessment and follow-up 4 strata assessment. In the 3-strata assessment, FC is considered alongside symptoms, clinical signs of heart failure, functional assessments (6MWD and CPET), blood tests (BNP or NT-	

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		proBNP), imaging (echocardiography, cMRI) and invasive measures of haemodynamics. In the 4-strata assessment, FC is considered alongside 6MWD and BNP or NT-proBNP. In clinical trials of sotatercept, participants were classified according to functional class, whether or not symptomatic, time since diagnosis and risk score. In which populations would sotatercept be used? - Sotatercept would be used in prevalent iPAH patients in the intermediate-high category who were failing on oral triple therapy and were not suitable for iv therapy. In this group the risk of polypharmacy and cumulative adverse event profiles must be considered against potential benefit. Given the risk of a bleeding event, this would not be suitable for those at increased risk of bleeding, for example peri-procedure, with concomitant comorbidity or the elderly.	
	NHS England	Where do you consider sotatercept will fit into the existing care pathway for PAH? Based on current evidence, service leads would consider sotatercept for newly diagnosed patients at the first follow-up assessment at 3- 4 months (patients will be on combination oral therapy (PDE5i and ERA or parenteral prostanoid usually in combination) where it would be used as an additional therapy for patients who had not met their treatment goal. For prevalent patients with PAH the majority who are likely to be established on combination therapy (PDE5i + ERA , PDE5i + ERA + selexipag, Riociguat ERA or parenteral prostanoid in combination with ERA/PDE5i/riociguat) where it may be considered as an additional therapy. Depending on treatment response it may be possible to consider reviewing other PAH medications.	Thank you for your comments.

		There is currently no data accessing efficacy at initial diagnosis but this may be considered in the future dependent on the results of further study. Have all the relevant comparators been included in the scope? Lung transplantation should be considered as access to sotatercept would arguably reduce or delay the need for transplantation. What is standard of care for PAH? Current standard care for PAH in the UK would be combination therapy with PDE5 or riociguat in combination with ERA +/- prostanoid (selexipag/epoprostenol/iloprost) What is the accepted definition of background therapy in the context of PAH? Background therapy should include diurectics, oxygen, treatment of comorbidities and in small number of patients anticoagulation. Is the World Health Organization (WHO) Functional Class measure used to determine which treatments people with PAH would be offered? Rather than relying on WHO FC alone a multiparameter approach (Humbert ESC/ERS Guidelines EHJ 2023) is now advised with an aim of achieving a low risk status for patients with PAH (IPAH and PAH-CTD) and where co-morbidities (lung, >=3 cardiac comorbities are present an intermediate low risk status has been suggested as appropriate treatment goal. In clinical trials of sotatercept, participants were classified according to functional class, whether or not symptomatic, time since diagnosis and risk score. In which populations would sotatercept be used?	

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		Rather than relying on WHO FC alone a multiparameter approach (Humbert ESC/ERS Guidelines EHJ 2023) is now advised with an aim of achieving a low risk status for patients with PAH (IPAH and PAH-CTD) and where co-morbidities (lung, >=3 cardiac comorbities are present an intermediate low risk status has been suggested as appropriate treatment goal. Would sotatercept be a candidate for managed access? Yes – use is restricted to a small number of nationally commissioned specialised services based in large teaching hospitals with good audit data that is published annually. Do you consider that the use of sotatercept can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Consideration should be given to the incremental value of this treatment observed in the studies despite patients being on drugs that target 2 or 3 of the current pathways. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. Published evidence and also a number of on-going trials which will report over next 2- 3 years examining the use of sotatercept in particular groups of patients eg at diagnosis, within first year of diagnosis and defined by particular risk groups.	

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		Note that sotatercept is administered by sub-cutaneous injection. As most patients are managed at home, consideration should be given to those unable to self-administer and without carer support.	
Additional comments on the draft scope	MSD (company)	The “Related NICE Guidelines” should be removed as they are not relevant for PAH therapy in this appraisal. The “Related National Policy” section should include the NHS England commissioning policies of relevance to this indication including: • Targeted Therapies for Pulmonary Hypertension Functional Class II, April 2013, NHSCB/A11/P/a. • Targeted Therapies for use in Pulmonary Hypertension in Adults, July 2015, A11/P/c. • Riociguat for pulmonary arterial hypertension, February 2017, 16055/P. Selexipag for treating pulmonary arterial hypertension (adults), December 2018, 170104P.	Thank you for your comments. The related NICE guidelines referred to have been removed from the scope. The suggested related national policies have been included.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

Asthma and Lung UK

PHA UK