CLINICAL PRIORITIES ADVISORY GROUP
06 and 07 November 2018

Agenda Item No	04.6
National Programme	Internal Medicine
Clinical Reference Group	Specialised Respiratory
URN	170104P

Title
Selexipag for treating pulmonary arterial hypertension (PAH) in adults

Actions Requested	1. Recommend the policy proposition
	2. Recommend the relative priority

Proposition
Selexipag is licensed for the long-term treatment of Pulmonary Arterial Hypertension (PAH) which is a rare condition. Selexipag has not been selected for a NICE technology appraisal and so the evidence has been considered through the NICE Commissioning Support Programme. It has previously been considered by CPAG (May 2018) and although there was evidence of effectiveness it was not prioritised for investment. Other prostanoid medicines that work on this pathway have to be inhaled or given intravenously on a continuous basis and are only commissioned for patients with severe disease late in the treatment pathway. Only about 9% of patients receive prostaglandin treatments currently. This proposition would make selexipag which is in a tablet form available to a specific subgroup of patients, those with more severe forms of the disease called (FCIII) and whose disease remains inadequately controlled despite already receiving two other therapies for PAH. When added to PDE5-inhibitor plus ERA therapy, selexipag has been shown to slow down progression of PAH and reduce hospitalisations caused by PAH compared with placebo. Inhaled and intravenous prostanoid treatments are complicated to administer as they require a strict regimen to be followed for safe use and are time-consuming for patients to administer. It is proposed Selexipag should be used earlier in the treatment pathway than inhaled or intravenous prostanoids with the aim of delaying deterioration, and because it is a tablet and relatively easy for patients to take. The cohort of patients who could receive selexipag includes those who are unable to manage administration of inhaled or IV, such as older people, or those with disabilities, as well as selected patients with FCIII disease.

This proposition is, as stated above, specific to a subgroup of the licensed population.

Clinical panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy proposition.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care Board has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Operational Delivery Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

The Benefits of the Proposition		
No	*Metric*	*Summary from evidence review*
1.	Survival	The main selexipag study (GRIPHON; Sitbon et al. 2015, n=1,156) measured death up to the end of the study both specifically due to PAH, and also due to any cause. When compared with placebo there was no statistically significant difference in either death from any cause (hazard ratio (HR) 0.97, 95% confidence interval (CI): 0.74 to 1.28, p=0.42) or death due to PAH (HR 0.86, 95% CI: 0.63 to 1.18, p=0.18). The results suggest that there is no statistically significant

		difference between the 2 groups for either mortality outcome. When compared with placebo there was no statistically significant difference in either death from any cause (hazard ratio (HR) 0.97, 95% confidence interval (CI): 0.74 to 1.28, p=0.42) or death due to PAH (HR 0.86, 95% CI: 0.63 to 1.18, p=0.18). The authors stated these results should be interpreted as exploratory because people may have received other treatments for PAH, including a significant proportion of people in the placebo group who went on to receive selexipag (50% of those also receiving ERA plus PDE5-inhiitor therapy who experienced a non-fatal primary endpoint [Coghlan et al. 2018]), which may have disguised the treatment effect. Also the European public assessment report (EPAR) stated that the mortality data is complex to assess, with some results showing selexipag had a negative effect, a neutral affect, and a best case scenario positive effect of up to a 25% reduction, on mortality. They noted that these models should, however, be interpreted with caution because in any such model assumptions have to be made.
2.	Progression free survival	The main study (Sitbon et al. 2015) used a composite outcome measure. This composite outcome is a combination of clinical events that might happen including hospitalisation due to PAH, disease progression, and death from any cause, where any one of those events would count as part of the composite. Hospitalisation, disease progression and death are strong signs of deterioration of PAH. Taken together these events occurred in 39% (227/582) of patients on placebo and 25% (144/574) of those treated with selexipag. In an analysis which examined the individual components of the composite outcome separately and as reported in the EPAR, patients in the selexipag group showed a statistically significantly lower risk of disease progression (6.6% vs. 17.2%; p<0.0001) and of hospitalisation for PAH worsening (13.6% vs. 18.7%; p=0.0402) than patients in the placebo group. These results suggest that selexipag can reduce the risk of PAH getting worse or prolong the time that patients are alive before their PAH worsens (often known as progression-free survival) compared with placebo. These results should be interpreted in the context that the composite outcome measure was designed to be analysed as a 'whole', and not for the individual components to be analysed separately.

3.	Mobility	
4.	Self-care	
5.	Usual activities	
6.	Pain	
7.	Anxiety / Depression	
8.	Replacement of more toxic treatment	
9.	Dependency on care giver / supporting independence	
10.	Safety	<u>All adverse events</u> The main study (Sitbon et al. 2015, =1,156) stated that 43.8% (n=252) of people receiving selexipag and 47.1% (n=272) of people receiving placebo reported ≥1 serious adverse events. A statistically significantly higher proportion of people stopped taking selexipag due to adverse events compared with placebo; 14.3% (n=82) and 7.1% (n=41) respectively ($p<0.001$). The most frequent adverse events leading people to stop taking selexipag were headache (3.3%), diarrhoea (2.3%) and nausea (1.7%). Death from any cause was 28 patients (4.9%) in the selexipag group and 18 patients (3.1%) in the placebo group. However, when assessing this data, the EPAR stated that "the observed increased mortality in the primary MM endpoint analysis is most likely due to informative censoring and/or a chance finding and lacks biological or clinical plausibility". The results from the study suggest that most people treated with selexipag may experience an adverse event with around 14% experiencing an adverse event leading to stopping treatment. Results should be interpreted with caution because some people were not on any background treatments, and others were on varying, locally determined background therapies before starting additional treatment with either selexipag or placebo. This may disguise the true effect of selexipag on adverse events.
11.	Delivery of	Selexipag is an oral tablet treatment taken twice a day.

	intervention	

Other health metrics determined by the evidence review		
No	Metric	Summary from evidence review
1	Composite of death or complication related to pulmonary arterial hypertension (PAH)	This composite outcome is a combination of clinical events that might happen including hospitalisation, disease progression, and death from any cause, where any one of those events would count as part of the composite. Patients with PAH have an increased risk of morbidity and mortality. Sitbon et al. (2015) showed that selexipag statistically significantly reduced the risk of the composite outcome occurring when compared with placebo with a rate of 27.0% for selexipag compared with 41.6% for placebo, HR 0.60 (99% CI: 0.46 to 0.78) p<0.001.This analysis reflects a 3-year follow-up period from starting treatment. The evidence suggests that selexipag results in a lowering in the risk of a morbidity or mortality event occurring. This result was supported by a sub group analysis (Gaine et al. 2017) for people with PAH associated with connective tissue disease. A similar result was also seen in the sub-group analysis (Coghlan et al. 2018) in patients already receiving double combination therapy with a PDE5-inhibitor and an ERA. The composite outcome contains a number of subjective components (although steps were taken to address this weakness, including adjudication by a blinded 3-person panel, and the disease progression component was very strictly defined). The use of a composite mortality/morbidity outcome is “encouraged” by the European Medicines Agency in PAH. The EPAR stated that the outcome is statistically significant and clinically relevant, but causes issues when assessing the true effect of selexipag on all-cause mortality.
2	Hospitalisations due to PAH	Hospitalisation for PAH is a strong indicator that the disease is worsening. Reducing hospitalisation is an important benefit for patients (and their carers) given the negative impact that being in hospital can have on the lives of both, and the fact that PAH-related hospitalisation is associated with an increased risk of death. In the main study (Sitbon et al. 2015), selexipag reduced the risk of a hospitalisation for PAH occurring (as a first outcome event) compared with placebo (13.6% vs. 18.7%; HR 0.67 [99% CI: 0.46 to 0.98], p=0.0402). As reported in the EPAR, when all hospitalisations due to PAH were analysed

		(irrespective of whether they occurred as a first outcome event or subsequently), hospitalisation for PAH was observed in 15% of people receiving selexipag compared with 21% of those on placebo. Similar findings were seen in the subgroup analyses by Coghlan et al. (2018) in patients already receiving combination therapy with a PDE5-inhiitor and an ERA, and by Gaine et al. (2017) in patients with PAH associated with connective tissue disease. Results suggest selexipag may help to reduce the risk of hospitalisation due to PAH. These results should be interpreted in the context that the composite outcome measure was designed to be analysed as a 'whole', and not for the individual components to be analysed separately.
3	Pulmonary vascular resistance (PVR)	PAH causes the tiny arteries in the lungs to become narrow or blocked making it harder for blood to flow through them. PVR is the resistance that must be overcome to push blood through the pulmonary circulatory system and create flow. The primary analysis for PVR in Simonneau et al. (2012) (n=43) was based on the per protocol set (all patients who did not violate the protocol in a way that might influence the evaluation of the effect of the drug). This showed a statistically significant reduction in PVR at 17 weeks follow-up for patients receiving selexipag (on top of an ERA and/or a PDE5-inhibitor) compared with placebo, with an average treatment effect of -33% (95% CI -47 to -15.2) p=0.0022. This result was supported by Tanabe et al. (2017) (n=33). A sensitivity analysis on the intent-to-treat population (all patients who received at least one dose of study drug) confirmed this analysis (Simonneau et al. 2012). The evidence indicates that receiving selexipag reduces the resistance in these arteries by somewhere between 15.2 to 47%, which will allow increased blood flow, a reduction in lung blood pressure, alleviation of the symptoms of PAH, and a reduction in the risk of heart failure. Evidence from the Tanabe study should be interpreted with more caution because the study may not have been sufficiently powered due to the number of people involved for statistical analyses and therefore be treated as descriptive only.
4	6 minute walking distance (6MWD)	6MWD measures the distance an individual is able to walk over a total of 6 minutes on a hard, flat surface. Symptoms of people with PAH include shortness of breath when undertaking mild exercise and the 6MWD test is a measure of how well patients can cope with this.

		Sitbon et al. (2015) reported a statistically significant improvement for selexipag of 12 metres (99% CI: 1 to 24), p=0.003 in median walking distance when compared with placebo at 26 weeks follow up. This result was supported by 2 smaller studies; Simonneau et al. (2012) (an increase of 24.7 metres with selexipag versus 0.4 metres with placebo although the result was not statistically significant) and Tanabe et al. (2017). The evidence suggests that receiving selexipag statistically significantly improves the ability of patients to undertake mild exercise with improved functional capacity. Results should be interpreted with caution because values were assigned to 21.6% of patients in the study who could not be measured by the authors. Missing values were determined based on strict criteria outlined within the study, however they were not based on actual patient data, which may add uncertainty to the findings. Additionally, the Simonneau study was not powered for this secondary endpoint.
5	Change in World Health Organisation (WHO) functional class	WHO functional class describes how severe a patient's pulmonary hypertension (PH) is. There are four different classes: I is the mildest and IV the most severe form of PH. Improvement in functional class indicates an improvement in the symptoms the patient is experiencing. Sitbon et al. (2015) reported no significant change in WHO functional class of patients (measured as an absence of worsening in functional class) when compared with placebo at 26 weeks follow up. Odds Ratio (OR) 1.16 (99% CI: 0.81 to 1.66) p=0.28. The evidence from Sitbon et al. (2015) suggests that selexipag neither improves nor decreases the functional class of patients. This result was supported by 2 smaller studies; Simonneau et al. (2012) and Tanabe et al. (2017). Results should be interpreted with caution because values were assigned to 18.3% of patients in the study who could not be measured by the authors. Missing values were determined based on criteria outlined in the study, however they were not based on actual patient data, which may add uncertainty to the findings.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
This policy proposition recommends selexipag for a selected group of patients with pulmonary arterial hypertension which is within its licensed indication. The policy will cover adults only as the Marketing Authorisation states that it is currently not recommended in patients under the age of 18. It is excluded from tariff.

Considerations from review by National Programme of Care Board
The proposal received the full support of the Internal Medicine NPoC Board virtual business meeting and was signed off at the Board Meeting on 27th September 2018.