NHS England

Evidence Review:

Selexipag in the treatment of Pulmonary Arterial Hypertension

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Contents

1. Introduction

Pulmonary arterial hypertension (PAH) is a rare and debilitating chronic disease of the pulmonary vasculature, characterised by vascular proliferation and remodelling of the small pulmonary arteries. This results in a progressive increase in pulmonary vascular resistance (PVR) which can ultimately lead to right heart failure and premature death. PAH is a progressive illness; if not diagnosed early and/or left untreated, the patient condition will deteriorate rapidly, leading to premature mortality in all aetiologies.

PAH can be classified into five etiological subgroups including; idiopathic, heritable, drug and toxin induced, associated, and persistent pulmonary hypertension of the newborn. In addition, PAH is typically scored on the basis of the severity of PAH-specific symptoms into four different World Health Organisation (WHO) functional classes. This system allows clinicians to make accurate differential diagnoses among diseases that demonstrate similarities in clinical presentation and pathophysiology, and helps to guide their decisions regarding appropriate treatment.

PAH has been shown to respond to targeted therapy and there are a number of different treatments available for PAH as set out in the clinical commissioning policies for pulmonary hypertension (see Section 12: Documents which have informed this policy).

This policy proposition considers the role of selexipag, an orally available prostacyclin receptor agonist, in the treatment of PAH in the context of the existing policy.

2. Summary of results

This evidence review was undertaken to answer the following questions:

1. Is selexipag (monotherapy or combined with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor or both ERA and PDE-5) clinically effective compared with no intervention or with other standardised treatments?
2. Is selexipag (monotherapy or combined with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor or both ERA and PDE-5) safe to use in the treatment of worsening PAH?
3. Is selexipag (monotherapy or combined with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor) cost effective in patients with pulmonary arterial hypertension? Are there any papers including a risk-benefit analysis?

Summary:
The current body of evidence for selexipag use in Pulmonary Arterial Hypertension (PAH) is based on one large, industry-sponsored Phase III trial and another small non-independent, randomised, proof of concept Phase II trial. While both studies appear to indicate some improvement with selexipag for 6 minutes walking distance, the functional significance of this improvement is not clear. The large, randomised Phase III trial also shows reduction in death or hospitalisation due to PAH. The same study also indicates lack of significant impact on preventing further deterioration of symptoms and all-cause mortality. Although some of the study participants were on alternate therapeutic interventions for PAH, there was no data on comparative clinical effectiveness amongst various drugs. There were no studies on cost effectiveness of selexipag. Further studies with clearly defined clinical endpoints and longer follow-up will be beneficial in providing conclusive evidence for the use of selexipag.

1. Is selexipag (monotherapy or combined with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor or both ERA and PDE-5) clinically effective compared with no intervention or with other standardised treatments?

The recently published finding from the Prostacyclin Receptor Agonist In Pulmonary Arterial Hypertension (GRIPHON) trial, a randomised, double blind, placebo controlled study is the most pivotal evidence available for selexipag use in PAH (Sitbon et al, 2015). This is a large industry-sponsored trial involving 1156 patients in 39 countries. The primary endpoint was defined as a composite index comprising of events of death from any cause or complications related to pulmonary arterial hypertension. This primary endpoint occurred in 397 patients, with significantly less events among patients in the selexipag group (27%), compared to placebo (41.6%) group (selexipag vs the placebo: hazard ratio 0.60; 99% confidence interval 0.46 - 0.78; P<0.001). This was in line with the higher death or hospitalisation due to worsening of PAH occurring in fewer patients in the selexipag group (102 patients, 17.8%, hazard ratio 0.70; 95% CI, 0.54 to 0.91; P = 0.003), compared to the placebo group (137 patients, 23.5%) during the study.

However, there was no difference in the all-cause mortality or reduction in deterioration of symptoms (no worsening WHO class) between the two groups. The all-cause mortality and worsening of WHO class formed part of the primary end point composite index and were also considered individually as secondary end points. The composite index contained a number of subjective components, as pointed out by the authors as a limitation of the study, and remains to be validated as a summary measure for clinical effectiveness.

As part of the primary endpoint composite index and as a secondary endpoint, the 6-minute walk distance was reported to be decreased by a median of 9.0 m from baseline in the placebo group and had increased by 4.0 m from baseline in the selexipag group at 26 weeks of treatment (treatment effect, 12.0 m; 99% CI, 1 to 24; P = 0.003). The functional significance of this magnitude of improvement and comparison with other therapeutic alternatives is not clear.

Preceding evidence for GRIPHON trial came from a 17 week, proof-of-concept, Phase 2, randomised, double-blind, placebo-controlled trial of 43 patients (Simonneau et al, 2012). Based on this study the intervention group has a statistically significant fall in pulmonary vascular resistance at week 17. Although there was a positive trend for some secondary outcome measures the difference was not statistically significant. The secondary outcome measures included 6-minute walk distance, aggravation of PAH, exploratory endpoints including Borg dyspnoea score, WHO Functional Class, and N-terminal pro brain natriuretic peptide.

2. Is selexipag (monotherapy or combined with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor or both ERA and PDE-5) safe to use in the treatment of worsening PAH?

Evidence so far indicates that selexipag is generally well tolerated. In the small patient population, Simonneau et al (2012) reported similar adverse event rates between selexipag and placebo groups and there were no deaths at a relatively short follow-up of 17 weeks. In GRIPHON Phase III, 41 patients (7.1%) in the placebo group and 82 patients (14.3%) in the selexipag group discontinued their study regimen prematurely because of an adverse event. The most frequent adverse events leading to discontinuation in the selexipag group were headache (in 3.3% of the patients), diarrhoea (in 2.3%), and nausea (in 1.7%). Hyperthyroidism occurred in 8 patients in the selexipag group and led to treatment discontinuation in 1 patient. No serious adverse events were reported more frequently (i.e., at a rate >1% higher than placebo group) in the selexipag group (Sitbon et al, 2015).

During the GRIPHON trial, selexipag was administered orally in individualized doses with a maximum allowable dose of 1600 µg twice daily. In the initial dose adjustment phase (12 weeks), the drug was initiated at a dose of 200 µg twice daily and increased weekly in twice-daily increments of 200 µg until unmanageable adverse effects associated with prostacyclin use, such as headache or jaw pain, developed . The dose was then decreased by 200 µg in both daily doses, and this reduced dose was considered to be the maximum tolerated dose for that patient. Adverse events associated with the drug occurred more frequently during the dose-adjustment phase.

Simonneau et al (2012) noted that as selexipag is orally available with a relatively long elimination half-life of 7.9 hrs it could help in improving pharmacokinetics, safety and ease of administration compared to need for IV administration of available prostacyclin agonists. This aspect was not specifically tested in the two studies.

3. Is selexipag (monotherapy or combined with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor) cost effective in patients with pulmonary arterial hypertension? Are there any papers including a risk-benefit analysis?

Currently, there is no evidence comparing effectiveness and cost effectiveness of selexipag with other drugs used in the management of pulmonary hypertension. Although GRIPHON Phase III study enrolled participants on stable dosage of endothelin-receptor antagonist, a phosphodiesterase type 5 inhibitor, or both, there was no analysis of comparative clinical impact of selexipag with these drugs.

3. Research questions

• Is selexipag (monotherapy or combined with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor or both ERA and PDE-5) clinically effective compared with no intervention or with other standardised treatments?

• Is selexipag (monotherapy or combined with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor or both ERA and PDE-5) safe to use in the treatment of worsening PAH?

• Is selexipag (monotherapy or combined with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor) cost effective in patients with pulmonary arterial hypertension? Are there any papers including a risk-benefit analysis?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

Grade	Study design and			Outcomes							Reference	Other		
Grade of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Study Endpoint	Study Endpoint Result	Reference	Complications noted	Benefits noted	Comments
1-	0	43 adult patients with symptomatic PAH. Selexipag =33 and placebo =10	Eligible patients received Selexipag 200 mg twice daily or matching placebo on day 1. Dosage was then up-titrated to 400 mg twice daily on day 3, to 600 mg twice daily on day 7, and to 800 mg twice daily on day 21. A slower up-titration schedule was allowed up to day 35 and final dosage was required to be stable for ≥4 weeks prior to evaluation at week 17	Clinical effectiveness of the intervention	Change in Pulmonary Vasculature Resistance (PVR) at week 17 expressed as a percentage of the baseline value and summarised using geometric mean and its 95% two-sided confidence limits (CL)	At week 17, PVR in the Selexipag group was 818.8 ± 416.9, a reduction of 129.8 ± 309.7 from baseline value of 948.6 ± 428.0. In placebo group the PVR at week 17 was 1090.8±421.3, an increase of 223.6±355.4 from baseline value of 867.2±379.3. The change in geometric mean expressed as a percentage of the baseline value, 95% CL) in the Selexipag and placebo groups was 80.7% (72.8–89.6%; n=29) and 115.9% (106.5–126.1%; n=6), respectively. This represented a statistically significant treatment effect of -30.3% (-44.7–-12.2%; Wilcoxon rank sum test p=0.0045).	6-min walk distance, aggravation of PAH (defined as death, transplantation, hospitalisation due to worsening PAH, or aggravation of PAH symptoms, i.e. a ≥10% deterioration in 6-min walk distance or the need for additional PAH-specific therapies, exploratory end-points including Borg dyspnoea score, WHO FC, and plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration	At week 17, the mean (95%CL) (change from baseline in 6-min walk distance was higher in the Selexipag group than placebo but the difference was not statistically significant, [+24.7 (-1.6–50.9) m in the Selexipag group and +0.4 (-19.7–20.5) m in the placebo group]. One (3.0%) Selexipag-treated patient and two (20.0%) placebo treated patients experienced aggravation of PAH. Five (15.6%) Selexipag-treated patients experienced an improvement in WHO FC, compared with one (10.0%) placebo recipient. Two patients in each group experienced a worsening of WHO FC. There was no difference between treatments with respect to Borg dyspnoea score (mean treatment effect -0.1 units, 95% CL -1.4–1.1) or plasma NT-proBNP (mean treatment effect -212.8 pg?mL-1, 95% CL -1,012.1–586.5 pg?mL-1).	-	-	Simonneau, Gérald; Torbicki, Adam; Hoeper, Marius M.; Delcroix, Marion; Karlócai, Kristóf; Galiè, Nazzareno; Degano, Bruno; Bonderman, Diana; Kurzyna, Marcin; Efficace, Michela; Giorgino, Ruben; Lang, Irene M.. Selexipag: an oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. Eur. Respir. J. 2012;40(4):874-880.	Both treatment groups experienced at least one adverse event, with headache, pain in jaw, pain in an extremity, nausea. Nasopharyngitis was the most frequently reported in the Selexipag group. The majority of adverse events in the Selexipag group were classified as mild (n=5; 15.2%) or moderate (n=20; 60.6%). Six (18.2%) patients in the Selexipag group and four (40.0%) in the placebo groups experienced at least one serious adverse event.	There was a statistically significant difference between the intervention and placebo group for change from baseline PVR. However there was no corresponding significant improvement for secondary outcomes. The authors note that the study was not powered to detect difference in secondary outcome measures.	Patient population: Symptomatic PAH of idiopathic or hereditary origin, associated with connective tissue diseases (PAH-CTD), corrected congenital heart disease (congenital systemic-to-pulmonary shunts surgically repaired 5yrs previously),oranorexigen use. Background targeted treatment with endothelin receptor antagonists (ERAs) and/or phosphodiesterase type 5(PDE-5) inhibitors was mandatory and patients had to have been on stable doses for 12 weeks before screening. Patients were required to have a baseline Pulmonary Vascular Resistance (PVR) of .400 dyn.s.cm-5, and two 6-min walk tests of 150–500 m inclusive and within ±15% of each other. Comments: This is a multicentre, multinational, proof-of-concept, phase 2, randomised, double-blind, placebo-controlled, parallel-group trial of 17 weeks duration. There was a good description of patient selection criteria including inclusion and exclusion criteria, intervention with dosage levels, blinding methodology, primary and secondary end point measures. Statistical analysis included analysis by per protocol set for primary end point and all-treated set for secondary end points. The results show that compared to placebo there was a statistically significant improvement in PVR at week 17 using Selexipag. However there was no such improvement for secondary end points, albeit there was positive trend for some secondary measures. Authors claim the study was not powered to detect changes in secondary points which is acceptable. Both treatment groups experienced at least one adverse event, with headache, pain in jaw, pain in an extremity, nausea. Nasopharyngitis was the most frequently reported in the Selexipag group. The majority of adverse events in the Selexipag group were classified as mild (n=5; 15.2%) or moderate (n=20; 60.6%). Six (18.2%) patients in the Selexipag group and four (40.0%) in the placebo groups experienced at least one serious adverse event. Authors claim that benefits of Selexipag were observed despite receiving background therapy with ERA and / or sildenafil but there is no data to support this claim. This is important given the need for combination treatment in patients who fail to respond to monotherapy. The ability to generalise from the study is further limited by 3:1 randomisation ratio, small sample size and drop-out rate. Currently there is one unpublished (available only as journal abstract) phase III (GRIPHON) study. This is large long-term outcome trial, studying a novel IP receptor agonist. The study enrolled 1156 patients in 181 participating centres in 39 countries. Primary efficacy results showed that Selexipag reduced the risk of a morbidity / mortality event by 39% compared with placebo (HR: 0.61; p < 0.0001). The efficacy of Selexipag was observed across key subgroups: age, gender, FC, PAH aetiology and background PAH therapy. Patients were treated for a period of up to 4.3 years.

1-	RCT multicenter, doubleblind, randomized, parallel-group, placebo-controlled, event-driven, phase 3 study	1156 (placebo (582 patients) or selexipag (574 patients)	Selexipag in individualized doses (maximum dose, 1600 µg twice daily).	Clinical effectiveness of the intervention	The primary end point was a composite of death from any cause or a complication related to pulmonary arterial hypertension up to the end of the treatment period (defined for each patient as 7 days after the date of the last intake of selexipag or placebo).	Primary end-point event occurred in 397 patients. 41.6% of those in the placebo group and 27.0% of those in the selexipag group (hazard ratio in the selexipag group as compared with the placebo group, 0.60; 99% CI 0.46 to 0.78; P<0.001).	1.Change in the 6-minute walk distance from baseline to week 26 . 2. The absence of worsening of WHO functional class from baseline to week 26. 3. All cause mortality up to the end of the study (time-to-event analysis).	1. At week 26, the 6-minute walk distance had decreased by a median of 9.0 m from baseline in the placebo group and had increased by 4.0 m from baseline in the selexipag group (treatment effect, 12.0 m; 99% CI, 1 to 24; P = 0.003). 2. At week 26, there was no significant difference between the placebo group and the selexipag group in the proportion of patients with no worsening in WHO functional class (74.9% and 77.8%, respectively; odds ratio, 1.16; 99% CI, 0.81 to 1.66; P = 0.28). 3. By the end of the treatment period, death due to pulmonary arterial hypertension or hospitalization for worsening of pulmonary arterial hypertension had occurred in 137 patients (23.5%) in the placebo group and in 102 patients (17.8%) in the selexipag group (hazard ratio in the selexipag group, 0.70; 95% CI, 0.54 to 0.91; P = 0.003); 87.4% of these events were hospitalizations 4. . By the end of the study, death from any cause had occurred in 105 patients (18.0%) in the placebo group and in 100 patients (17.4%) in the selexipag group (hazard ratio in the selexipag group, 0.97; 95% CI, 0.74 to 1.28; P = 0.42). Findings from a sensitivity analysis that assumed that patients with unknown vital status had died (4.8% of patients) were consistent with the findings of the main analysis of death from any cause .	Refer to outcomes	Refer to outcomes	Sitbon O, Channick R, Chin KM, Frey A, Gaine S, GaliÃ¨ N, Ghofrani HA, Hoeper MM, Lang IM, Preiss R, Rubin LJ, Di Scala L, Tapson V, Adzerikho I, Liu J, Moiseeva O, Zeng X, Simonneau G, McLaughlin VV; GRIPHON Investigators.. Selexipag for the Treatment of Pulmonary Arterial Hypertension. N Engl J Med 2015;373(26):2522-33.	41 patients (7.1%) in the placebo group and 82 patients (14.3%) in the selexipag group discontinued their study regimen prematurely because of an adverse event. The most frequent adverse events leading to discontinuation in the selexipag group (events for which there was >1% difference between the selexipag and placebo groups) were headache (in 3.3% of the patients), diarrhea (in 2.3%), and nausea (in 1.7%). Hyperthyroidism occurred in 8 patients in the selexipag group and led to treatment discontinuation in 1 patient. No serious adverse events were reported more frequently (i.e., at a rate >1% higher) in the selexipag group than in the placebo group.	Refer to outcomes	Patient population: Patients ranged between 18-75 years; At baseline: 21.3% were not receiving treatment for PAH, 13.1% were receiving stable-doses of ERAs, 31.8% were receiving stable doses of PDE-5 inhibitors, and 33.8% were receiving stable doses of ERA and PDE-5. Comments: This study was not independently funded. The key limitation of the study is the composite index used for primary outcome which contains a number of subjective components and remains to be validated as a summary measure for clinical effectiveness. Authors note that it was based on recommendations for primary end points in pivotal randomized controlled trials in pulmonary arterial hypertension. To address this potential limitation, the disease progression component was stringently defined and all events were adjudicated by a three-person critical-event committee. It should however be noted that while the composite primary endpoint showed significantly better results with selexipag, there was no difference in the all-cause mortality. In addition, the authors point out the potential for response bias as the study included an optional post-treatment observation period after placebo or selexipag was discontinued. The follow-up of patients who discontinued placebo or selexipag was also reported as limited. In addition to this, 18.9% of patients discontinued placebo or selexipag prematurely. This rate of premature discontinuation was planned for in the study design and sensitivity analysis was undertaken to check for consistency of results.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	Date limits: Non-specific Inclusion Criteria: • Male and female patients 18-75 years old, with symptomatic PAH. • PAH belonging to the following subgroups (Idiopathic, or Heritable, or Drug or toxin induced, or Associated (APAH) with Connective tissue disease, Congenital heart disease with simple systemic-to-pulmonary shunt at least 1 year after surgical repair, or HIV infection). • Documented hemodynamic diagnosis of PAH by right heart catheterization, performed at any time prior to Screening. • Six minute walk distance (6MWD) between 50 and 450 m at Screening within 2 weeks prior to the Baseline Visit. Exclusion Criteria: • Patients with pulmonary hypertension (PH) in the Updated Dana Point Classification Groups 2-5, and PAH Group 1 subgroups that are not covered by the inclusion criteria. • Patients who have received prostacyclin or its analogs within 1 month before Baseline Visit, or are scheduled to receive any of these compounds during the trial. • Patients with moderate or severe obstructive lung disease • Patients with moderate or severe restrictive lung disease • Patients with moderate or severe hepatic impairment (Child-Pugh B and C). • Patients with documented left ventricular dysfunction • Patients with severe renal insufficiency. • Patients with BMI <18.5 Kg/m2. • Patients who are receiving or have been receiving any investigational drugs within 1 month before the Baseline Visit. • Acute or chronic impairment (other than dyspnea), limiting the ability to comply with study requirements, in particular with 6MWT Recently conducted or planned cardio-pulmonary rehabilitation program based on exercise training. • Psychotic, addictive or other disorder limiting the ability to provide informed consent or to comply with study requirements. • Life expectancy less than 12 months. • Females who are lactating or pregnant or plan to become pregnant during the study.
Updated search terms - Population	Pulmonary arterial hypertension PAH Heritable Pulmonary Arterial Hypertension Idiopathic pulmonary hypertension Pph1 with Hht Primary pulmonary hypertension Pulmonary hypertension, primary 1 Pulmonary hypertension, primary , dexfenfluramine-associated Pulmonary hypertension, primary, fenfluramine-associated
Updated search terms - Intervention	Selexipag Uptravi ACT-293987 NS-304 Selective IP receptor agonist Selective prostacyclin receptor agonist

Updated search terms - Comparator	Epoprostenol Flolan PGI2 PGX Prostacyclin Prostaglandin I(2) Prostaglandin I2 Epoprostenol Sodium Platelet Aggregation Inhibitors Antihypertensive Agents Prostaglandin Iloprost Ciloprost Ventavis Sildenafil citrate ZK-36374 Sitaxsentan Vasodilator Agents Treprostinil Bosentan Ro 47-0203 Ro-47-0203 Tracleer Endothelin Receptor Antagonist
Updated search terms - Outcome	-
Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, the following are included: 1. All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2. All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reach 30, inclusion stops here 3. All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reach 30, inclusion stops here 4. All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reach 30, inclusion stops here 5. Expert opinion
	Specific inclusion criteria
	Inclusion of following article as per request of policy working group: Sitbon O, Channick R, Chin KM, Frey A, Gaine S, GaliÃ¨ N, Ghofrani HA, Hoeper MM, Lang IM, Preiss R, Rubin LJ, Di Scala L, Tapson V, Adzerikho I, Liu J, Moiseeva O, Zeng X, Simonneau G, McLaughlin VV; GRIPHON Investigators.. Selexipag for the Treatment of Pulmonary Arterial Hypertension. N Engl J Med 2015;373(26):2522-33.

Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Do not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (except where there are fewer than 10 studies overall) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site
	Specific exclusion criteria
	-