NHS England

Evidence Review:

Riociguat for Pulmonary Arterial Hypertension

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Contents

1. Introduction

Pulmonary hypertension (PH) is a rare disorder of the blood vessels in the lung, characterised by raised pressure in the pulmonary artery, which results in a range of
symptoms and may be life threatening. Pulmonary arterial hypertension (PAH) is a clinical condition characterised by the presence of pre-capillary PH in the absence of other causes of pre-capillary PH such as lung disease, chronic thromboembolism, or other rare causes. If the cause is unknown then it is referred to as idiopathic pulmonary arterial hypertension (IPAH). IPAH can occur sporadically or may be familial.

PAH is a rare and debilitating chronic disease of the pulmonary vasculature, which can occur at any age, has many causes, and always shortens life expectancy. PAH is characterised by extensive remodelling of the pulmonary circulation, where blood vessels become increasingly constricted leading to progressive pulmonary vascular resistance and increasing limitations on physical activity, right heart failure and premature death.

PAH is an orphan condition for which there is currently no cure, other than lung transplantation. In the early stages of the disease patients may be able to engage in normal physical activity without overt symptoms. However, as the disease progresses there will be marked limitations on physical activity with symptoms of breathlessness and fatigue. Eventually there will be an inability to carry out physical activity without symptoms. The later stages of the disease are associated with right heart failure.

Conventional therapies (e.g. diuretics) focus on managing symptoms attributed to PAH, whilst disease-targeted therapies act on the disease pathway itself focusing on clinical, functional and haemodynamic improvement. These therapies are considered effective when stasis in disease progression is achieved as improvements are often limited. As such, each patient's disease trajectory must be considered when analysing the effectiveness of the medication. Disease-targeting therapies currently include PDE5 inhibitors, endothelin receptor antagonists (ERA) and prostaglandins, often in varying combinations to achieve maximum clinical effect and are of proven prognostic benefit. This policy concerns the use of riociguat for the treatment of adults with pulmonary arterial hypertension (PAH) with World Health Organisation (WHO) Functional Class (FC) II or III.

Riociguat increases the sensitivity of soluble guanylate cyclase (sGC) to nitric oxide and can also stimulate sGC independently of nitric oxide, increasing the level of cyclic guanosine monophosphate (cGMP), resulting in vasorelaxation, antiproliferative and antifibrotic effects. Riociguat is licensed for use as a PAH-specific monotherapy and for use in combination with other PAH-specific therapies. Smoking whilst on riociguat has been shown to reduce the benefit of the medication and therefore all patients receiving riociguat will be offered access to smoking cessation assistance.

This policy concerns the use of riociguat as a substitute for currently commissioned therapies when these are inadequate or contraindicated, not in competition.

2. Summary of results

The search identified 154 articles of which 13 met the inclusion criteria for evidence review.

A large proportion of the papers related to in vitro studies considering cellular mechanisms of action, pharmacokinetic or animal studies. There were excluded as they were not directly relevant to the research questions.

A number of the studies related to patients with Chronic Thromboembolic Pulmonary Hypertension (CTEPH), as opposed to PAH. Relevant studies in a CTEPH population have been included with the aim to review evidence on safety or cost of riociguat.

The evidence is mostly characterised by studies graded as 1- (RCTs with a high risk of bias due to manufacturer involvement) or 2- (cohort studies with a high risk of bias). There are a number of randomised controlled trials (RCTs), but all are placebo controlled. The majority of the literature is sponsored by or linked to the drug manufacturer. It should be noted that the data available on currently commissioned treatments also arose from industry sponsored studies. The current body of evidence is lacking direct comparison of the risks and benefits of riociguat with currently established effective therapeutic agents for PAH, it remains difficult to conclude regarding comparative effectiveness and safety of the drug as a monotherapy or combination therapy.

Part 1: Clinical effectiveness of riociguat as a monotherapy compared with a PDE5 inhibitor or an ERA

PATENT1, a randomised double blind trial demonstrated a positive response to riociguat therapy (Ghofrani et al, 2013). This indicates that riociguat could be considered as first line therapy for patients. However, as none of the studies compared effectiveness and safety of riociguat to PDE5 inhibitor or an ERA the data is unable to provide information on comparative or superior effectiveness of riociguat. This this was a medium sized, commercially sponsored RCT, and is the study on which the European Medicines Agency (EMA) licence was granted. The patient population for this trial were group 1 PAH patients, of whom 42% were functional class II and 53% were functional class III. Patients were randomised to placebo, riociguat in individually adjusted doses of up to maximum 2.5 mg three times daily, or riociguat in individually adjusted doses up to maximum 1.5 mg three times daily. At week 12, the 6-minute walk distance had increased from baseline by a mean of 30 m in the 2.5 mg group and had decreased by a mean of 6 m in the placebo group. There was improvement in the primary outcome across both groups in the first eight weeks followed by reduction in the 6 minute walking distance in the placebo group between weeks eight and twelve. The study reported primary outcome only for 2.5mg dosage group and not the 1.25mg group. There were significant improvements in the specified secondary endpoints, including pulmonary vascular resistance, NT proBNP levels, functional class and time to clinical worsening, and Borg Dyspnoea score when comparing patients in the 2.5 mg riociguat group with the placebo group. Syncope, the most commonly occurring serious adverse event was higher in the placebo group (4%) compared to 1% in the riociguat group.

Of the total number of patients randomised (n=443), A total of 44% of the patients were receiving treatment with endothelin-receptor antagonists (primarily bosentan), and 6% were receiving prostanoid therapy (primarily inhaled iloprost); 50% were receiving no other treatment for pulmonary arterial hypertension. Patients who were receiving treatment with phosphodiesterase type 5 inhibitors or intravenous prostanoids were excluded. Further subgroup analysis showed that the functional benefits of riociguat therapy tended to be greater in patients who had previously received prostanoids. The study demonstrated that the addition of riociguat to an ERA in combination was both safe and met the primary end point so there is clear evidence that the addition of riociguat to an ERA is effective.

There is limited value of comparative efficacy data with subgroups comprising of small numbers of patients and lack of information on the statistical tests used to ensure that perceived outcomes are not due to a random variation.

Zheng et al (2014) reported a meta-analysis of a number of targeted therapies in the treatment of PAH. This study was excluded from the evidence review to avoid double counting of impact given the only paper relevant to this review that was included in the meta-analysis was Gofhrani et al (2013). Analysis of data from 18 trials with a total of 4363 subjects by indicates that phosphodiesterase type 5 inhibitors were associated with a statically significant reduction in mortality (RR 0.22; 95% CI 0.07-0.71, p = 0.011), while other drugs only showed a trend toward reducing mortality. Compared with placebo, endothelin receptor antagonists (ERAs), PDE-5Is and riociguat significantly reduced clinical worsening, ameliorated WHO function class, and increased the 6-min walk distance.

Rosenkranz et al (2015) reported an open label extension study to PATENT1 in a cohort of patients with PAH following repair of congenital heart disease. The authors conclude the drug is efficacious in this cohort compared to placebo and it is well tolerated. The authors note the exploratory nature of the study, given the small numbers and that the study is probably not appropriately powered to detect the differences reported. In addition, it should be noted the study is commercially sponsored.

Rubin et al (2015) reported on the one year extension study for the PATENT1 cohort. This was an observational follow up of the PATENT1 cohort. The study concluded that long-term riociguat was well tolerated in patients with pulmonary arterial hypertension, and led to sustained improvements in exercise capacity and functional capacity for up to one year.

Langleben et al (2015) aimed to investigate whether riociguat increased the proportion of patients achieving clinically relevant responder thresholds compared with placebo during PATENT1. In summary, the proportion of patients with a combination of response criteria (6MWD ≥ 380 m, WHO FC I/II, cardiac index ≥2.5 litre/min/m2, NT-proBNP < 1,800 pg/ml, and SvO2 ≥65%) was 15% and 13% at baseline in the riociguat group (n = 193) and the placebo group (n = 93), respectively. After 12 weeks of treatment, the proportion increased to 34% in the riociguat group, whereas it was largely unchanged in the placebo group (16%). Responders were reported to be younger (mean age 44 vs 53 years), be in a lower WHO FC (4/73/23/0% vs 4/34/60/1% in WHO FC I/II/III/IV, respectively) and have a lower BMI (24 vs 27) compared with non-responders.

Bonderman et al 2013 considered the efficacy of riociguat in a cohort with pulmonary hypertension caused by systolic left ventricular dysfunction. It was concluded that the primary end point of the study was not met but that riociguat was well tolerated in patients with pulmonary hypertension caused by systolic left ventricular dysfunction and improved cardiac index and pulmonary and systemic vascular resistance. This was a placebo controlled dose ranging study.

Bonderman et al 2014 published a small (46 screened, 39 randomised) phase 2a study in a population of PH patients and low ejection fraction. With the highest dose, 2mg, there was no significant difference in the primary outcome, and some reported statistically significant differences in the secondary outcomes. The extent to which these differences are clinically relevant is uncertain.

Part 2: Cost-effectiveness of riociguat as a monotherapy compared with a PDE5 inhibitor or an ERA

There was no economic analysis of riociguat.

It is worth highlighting the National Institute for Health Research (NIHR) sponsored a health technology assessment (HTA) considering the clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for pulmonary arterial hypertension (Chen et al 2009). This reports incremental cost-effectiveness ratios for these treatments, all close to or above the threshold.

There were two papers that were excluded from the clinical evidence review giving some insight into quality of life (QoL) gain, Minai et al (2015) – the CHEST study, and Mathai et al (2015) – the PATENT study. These would obviously be of use in a subsequent economic analysis. They were excluded on account of them being conference abstracts.

Burudpakdee et al (2014) reported the budgetary impact of adding riociguat to a hypothetical US population of 1 million for the treatment of patients with pulmonary arterial hypertension or CTEPH. The model estimated that 7 patients with PAH and 2 patients with CTEPH would be suitable for pharmacotherapy. Also the model estimated that the incremental per capita costs for coverage for riociguat were £0.18. This cost is for a Medicare insured population. As this was a US study some caution should be exercised in extrapolating this study to England.

Part 3: Clinical effectiveness of riociguat as a monotherapy compared with a PDE5 inhibitor and an ERA as dual therapy:

Almost all of the evidence did not adequately contextualise the treatment in a pathway of care, where distinctions were drawn between treatment naïve and prior treated, the numbers were too small to draw any meaningful conclusions.

Galie et al (2015), reported a small (n=18) RCT and noted that combination of riociguat and sildenafil, compared to sildenafil alone did not make a difference to the primary outcome (max change in supine systolic blood pressure (SBP) within 4 hours post administration) and there were some unfavourable safety signals reported. The authors recommend that concomitant use of riociguat with phosphodiesterase-5 inhibitors (PDE5I) is contraindicated.

Part 4: Clinical effectiveness of riociguat and an ERA as dual therapy compared with a PDE5 inhibitor and an ERA as dual therapy:

Some of the studies provided information on potential dual therapies. For example, Ghofrani (2013) included patients both previously treated with background prostanoids or endothelin receptor agonists and patients not previously treated. Sub group analyses showed that riociguat improved the 6-minute walking distance (primary outcome) both in patients who were receiving no other treatment for the disease and in those who were receiving ERA (N=194) or prostanoids (N=28) was pre-specified (i.e. not post hoc). Hence, it would appear that addition of riociguat to an ERA in combination was safe and met the primary end point. Further evidence on the superiority of ERA and riociguat versus an ERA alone is not available due to absence of direct comparison groups.

Part 5: Clinical effectiveness of riociguat and a prostaglandin as dual therapy or riociguat, a prostaglandin and an ERA as triple therapy, compared with a PDE5 inhibitor and a prostaglandin as dual therapy, or a PDE5 inhibitor, a prostaglandin and an ERA as triple therapy:

There was insufficient data to draw a meaningful conclusion on riociguat as a dual therapy in combination with a

prostaglandin or triple therapy with prostaglandin and an ERA. While 28 patients in PATENT1 trial received background prostanoids, the trial does not appear to be sufficiently powered for this sub group analysis due to the small number.

3. Research questions

1. In patients with WHO functional class II or III pulmonary arterial hypertension, is riociguat a clinically effective, safe and cost effective alternative first-line monotherapy when compared with a PDE5 inhibitor or an ERA?

2. In patients with WHO functional class II or III pulmonary arterial hypertension, currently being treated with a PDE5 inhibitor but failing to show continued benefit, is switching to riociguat monotherapy clinically effective, safe and more cost effective than adding an ERA to the failing PDE 5 inhibitor?

3. In patients with WHO functional class II or III pulmonary arterial hypertension, currently being treated with a combination of a PDE5 inhibitor and an ERA but failing to show continued benefit, is switching to riociguat in combination with an ERA clinically effective, safe and cost effective?

4. In patients with WHO functional class II or III pulmonary arterial hypertension, currently being treated with a combination of IV Prostaglandins and a PDE5 inhibitor but failing to show continued benefit, is switching to IV Prostaglandins in combination with riociguat clinically effective, safe and cost effective?

5. In patients with WHO functional class II or III pulmonary arterial hypertension, currently under consideration for lung transplantation and being treated with IV Prostaglandins, a PDE5 inhibitor and an ERA, is switching to the combination of IV Prostaglandins, riociguat and an ERA clinically effective, safe and cost effective?

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 intervention			Outcomes					Reference	Other		
Grade of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
N/a	Meta Analysis	4636	Targeted therapies - this was a review of many different targeted therapies	Clinical effectiveness of the intervention compared to existing interventions	N/a	N/a	N/a	N/a	Zheng, Ya-Guo; Ma, Hong; Hu, En-Ci; Liu, Gang; Chen, Guo; Xiong, Chang-Ming. Oral targeted therapies in the treatment of pulmonary arterial hypertension: a meta-analysis of clinical trials. Pulm Pharmacol Ther 2014;29(2):241-249.	na	na	Zheng et al (2014) reported a meta-analysis of a number of targeted therapies in the treatment of PAH. This study was excluded from the evidence review to avoid double counting of impact given the only paper relevant to this review that was included in the meta-analysis was Gofhrani et al (2013). Analysis of data from 18 trials with a total of 4363 subjects by indicates that phosphodiesterase type 5 inhibitors were associated with a statically significant reduction in mortality (RR 0.22; 95% CI 0.07-0.71, p = 0.011), while other drugs only showed a trend toward reducing mortality. Compared with placebo, endothelin receptor antagonists (ERAs), PDE-5Is and riociguat significantly reduced clinical worsening, ameliorated WHO function class, and increased the 6-min walk distance.
1-	RCT	39 (of 46 initially screened)	Riociguat (0.5, 1, or 2 mg)	Clinical effectiveness of the intervention compared to existing interventions	Efficacy variable was the peak decrease in mPAP from baseline up to 6 hours	There was no significant change in peak decrease in mPAP with riociguat 2mg (n = 10) vs placebo (n = 11, P = .6).	Hemodynamic and echocardiographic parameters, safety, and pharmacokinetics	Riociguat 2 mg significantly increased stroke volume (+9 mL [95% CI, 0.4-17]; P = .04) and decreased systolic BP (−12 mm Hg [95% CI, −22 to −1]; P = .03) and right ventricular end-diastolic area (−5.6 cm2 [95% CI, −11 to −0.3]; P = .04), without significantly changing heart rate, PAWP, transpulmonary pressure gradient, or pulmonary vascular resistance	Bonderman, Diana; Pretsch, Ingrid; Steringer-Mascherbauer, Regina; Jansa, Pavel; Rosenkranz, Stephan; Tufaro, Caroline; Bojic, Andja; Lam, Carolyn S. P.; Frey, Reiner; Ochan Kilama, Michael; Unger, Sigrun; Roessig, Lothar; Lang, Irene M.. Acute hemodynamic effects of riociguat in patients with pulmonary hypertension associated with diastolic heart failure (DILATE-1): a randomized, double-blind, placebo-controlled, single-dose study. Chest 2014;146(5):1274-1285.	none	none	This was a small (46 screened, 39 randomised) phase 2a study in a population of PH patients and low ejection fraction. With the highest dose - 2mg - there was no significant difference in the primary outcome, and some reported statistically significant differences in the secondary outcomes. The extent to which these differences are clinically relevant is uncertain.

1-	RCT	201	Riociguat (0.5, 1, or 2 mg 3 times daily) in three parallel arms (+ fourth placebo arm)	Clinical effectiveness of the intervention compared to existing interventions	Change in mean pulmonary artery pressure (mPAP) from baseline to week 16	The decrease in mean pulmonary artery pressure in the riociguat 2 mg group (-6.1±1.3 mm Hg; P<0.0001 versus baseline) was not significantly different from placebo (P=0.10)	Changes in hemodynamic and echocardiography parameters	Cardiac index (0.4 L·min(-1)·m(-2); 95% confidence interval, 0.2-0.5; P=0.0001) and stroke volume index (5.2 mL·m(-2); 95% confidence interval, 2.0-8.4; P=0.0018) were significantly increased without changes in heart rate or systemic blood pressure compared with placebo	Bonderman, Diana; Ghio, Stefano; Felix, Stephan B.; Ghofrani, Hossein-Ardeschir; Michelakis, Evangelos; Mitrovic, Veselin; Oudiz, Ronald J.; Boateng, Francis; Scalise, Andrea-Viviana; Roessig, Lothar; Semigran, Marc J.; Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension Riociguat Trial (LEPHT) Study Group. Riociguat for patients with pulmonary hypertension caused by systolic left ventricular dysfunction: a phase IIb double-blind, randomized, placebo-controlled, dose-ranging hemodynamic study. Circulation 2013;128(5):502-511.	none	none	This was a medium sized phase 2b study of patients with PAH (18 to 80yrs) who had HF resulting from ischemic or nonischemic causes (defined as LV ejection fraction ≤40%, and mPAP ≥25 mm Hg at rest (measured by right heart catheterization)) and were symptomatic despite optimized medical therapy according to published guidelines at a stable dose regimen for >30 days before randomization. The study concluded that primary end point of the study was not met but that riociguat was well tolerated in patients with pulmonary hypertension caused by systolic left ventricular dysfunction and improved cardiac index and pulmonary and systemic vascular resistance. This was a placebo controlled study.

1-	RCT	443	Riociguat administered in doses that were individually adjusted for each patient up to 2.5mg three times daily (2.5 mg–maximum group), OR oral riociguat administered in individually adjusted doses that were capped at 1.5 mg three times daily (1.5 mg–maximum group).	Clinical effectiveness of the intervention compared to existing interventions	Change from baseline to the end of week 12 in the distance walked in 6 minutes	The 6-minute walk distance had increased by a mean of 30 m in the 2.5 mg-maximum group and had decreased by a mean of 6 m in the placebo group (least-squares mean difference, 36 m; 95% confidence interval, 20 to 52; P<0.001).	Change in pulmonary vascular resistance, N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, World Health Organization (WHO) functional class, time to clinical worsening, score on the Borg dyspnoea scale, quality-of-life variables, and safety	There were significant improvements in pulmonary vascular resistance (P<0.001), NT-proBNP levels (P<0.001), WHO functional class (P=0.003), time to clinical worsening (P=0.005), and Borg dyspnoea score (P=0.002).	Ghofrani, Hossein-Ardeschir; Galiè, Nazzareno; Grimminger, Friedrich; Grünig, Ekkehard; Humbert, Marc; Jing, Zhi-Cheng; Keogh, Anne M.; Langleben, David; Kilama, Michael Ochan; Fritsch, Arno; Neuser, Dieter; Rubin, Lewis J.; PATENT-1 Study Group. Riociguat for the treatment of pulmonary arterial hypertension. N. Engl. J. Med. 2013;369(4):330-340.	The most common serious adverse event in the placebo group and the 2.5 mg-maximum group was syncope (4% and 1%, respectively).	none	This was a medium sized RCT of patients with symptomatic PAH (detail re aetiology is defined in the manuscript) with pulmonary vascular resistance greater than 300 dyn · sec · cm–5, a mean pulmonary-artery pressure of at least 25 mm Hg, and a 6-minute walk distance of 150 to 450 m. There is a risk of bias given the manufacturer involvement. The study concludes that in patients with symptomatic PAH who are not receiving treatment riociguat improves 6 minute walk distance - a net difference of 24 metres - and a number of other secondary endpoints. Drop out was comparable between the three groups. It is worth stating that up to week 8 there was improvement in the primary outcome across both groups - with a fall off in the 6m walk distance in the placebo group between week 8-12. It is also worth noting that the primary outcome seems to be reported for the 2.5mg group and not the 1.25mg group. This may warrant further investigation, it may have a bearing on dosing, side effect profile and cost effectiveness. The extent to which a 24 metre difference in 6 minute walk test is of real world clinical significance warrants further discussion. It is noted that patients who were receiving phosphodiesterase type 5 inhibitors were not eligible for inclusion in this study

1-	RCT	261	Riociguat - adjusted from a starting dose of 1 mg three times daily according to systolic systemic arterial pressure and signs or symptoms of hypotension (final range, 0.5 mg to 2.5 mg three times daily)	Clinical effectiveness of the intervention compared to existing interventions	Change from baseline to the end of week 16 in the distance walked in 6 minutes	At week 16, the 6-minute walk distance had increased from baseline by a mean of 39 metres in the riociguat group, as compared with a mean decrease of 6 metres in the placebo group - this is a difference of 45 metres in the 6 minute walk test between the two groups	Changes from baseline to the end of week 16 in pulmonary vascular resistance, N-terminal pro–brain natriuretic peptide (NT-proBNP) level, World Health Organization (WHO) functional class (an adaptation of the New York Heart Association functional classification), time to clinical worsening, Borg dyspnoea score , EQ-5D;Living with Pulmonary Hypertension (LPH) questionnaire score	Pulmonary vascular resistance decreased by 226 dyn·sec·cm–5 in the riociguat group, as compared with an increase of 23 dyn·sec·cm–5 in the placebo group. A number of other secondary endpoints are reported. Riociguat was also associated with significant improvement in other hemodynamic variables, including mean pulmonary-artery pressure and cardiac output. Levels of NT-proBNP were significantly reduced in patients treated with riociguat, and changes in WHO functional class at 16 weeks also significantly favoured riociguat. There was no significant difference in the incidence of clinical-worsening events between the riociguat and placebo groups (2% and 6%, respectively). On the basis of the prespecified hierarchical testing procedure, analyses of the Borg dyspnoea score and quality-of-life data were considered exploratory – the Borg dyspnoea score decreased by 0.8 points in the riociguat group and increased by 0.2 points in the placebo group (P=0.004). There was a nominally significant difference between the two groups in the change in the EQ-5D score but not in the change in the LPH questionnaire score.	Ghofrani, Hossein-Ardeschir; D'Armini, Andrea M.; Grimminger, Friedrich; Hoeper, Marius M.; Jansa, Pavel; Kim, Nick H.; Mayer, Eckhard; Simonneau, Gerald; Wilkins, Martin R.; Fritsch, Arno; Neuser, Dieter; Weimann, Gerrit; Wang, Chen; CHEST-1 Study Group. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N. Engl. J. Med. 2013;369(4):319-329.	The most frequently occurring serious adverse events were right ventricular failure (in 3% of patients in each group), syncope (in 2% of the riociguat group and 3% of the placebo group), and hemoptysis (in 2% of the riociguat group). Drug-related serious adverse events in the riociguat group included syncope in three patients (2%) and gastritis, acute renal failure, and hypotension in one patient each (1%); in the placebo group, syncope and trauma occurred in one patient each (1%).	Na	This was a medium sized RCT of patients with inoperable chronic thromboembolic pulmonary hypertension or persistent or recurrent pulmonary hypertension after pulmonary endarterectomy. There is a risk of bias given the manufacturer involvement. The study concludes that in patients with chronic thromboembolic pulmonary hypertension who were deemed to be ineligible for surgery or who had persistent or recurrent pulmonary hypertension after undergoing pulmonary endarterectomy improves 6 minute walk distance - a net difference of 45 metres - and a number of other secondary endpoints. Drop out was comparable between the three groups. The extent to which a 45 metre difference in 6 minute walk test is of real world clinical significance warrants further discussion.

2-	Cohort	35	Riociguat administered in doses that were individually adjusted for each patient up to 2.5 mg three times daily (2.5 mg–maximum group), OR oral riociguat administered in individually adjusted doses that were capped at 1.5 mg three times daily (1.5 mg–maximum group).	Clinical effectiveness of the intervention compared to existing interventions	6mWD at week 12	At week 12, 6mWD had increased by a mean ±SD of 60m in patients with PAH CHD. There was no change from baseline in the placebo group	PVR, NT-proBNP, WHO functional status	Patients in the 2.5mg group improved in all of the secondary variables compared to the placebo group	Rosenkranz, Stephan; Ghofrani, Hossein-Ardeschir; Beghetti, Maurice; Ivy, Dunbar; Frey, Reiner; Fritsch, Arno; Weimann, Gerrit; Saleh, Soundos; Apitz, Christian. Riociguat for pulmonary arterial hypertension associated with congenital heart disease. Heart 2015;101(22):1792-1799.	Six serious SAE were noted in four patients - none were related to the study drug by the investigators	na	This study was an open label extension study to PATENT1 in a cohort of patients with PAH following repair of congenital heart disease. The authors conclud that the drug is efficacious in this cohort compared to placebo and it is well tolerated. The authors note the exploratory nature of the study - given the small numbers and that the study is probably not appropriately powered to detect the differences reported. In addition, it should be noted the study is commercially sponsored.
1-	RCT	18	Sildenafil + riociguat (up to 2.5 mg three times daily) for 12 weeks	Clinical effectiveness of the intervention compared to existing interventions	Maximum change in supine systolic blood pressure (SBP) from baseline within 4 hours of dosing	No difference in maximum change in supine SBP from baseline within 4 hours between the riociguat and placebo groups	Additional blood pressure, heart rate and exploratory efficacy variables, and safety	Changes in standing SBP and supine or standing diastolic blood pressure were also not different. Combination therapy showed no favourable effects on exploratory clinical parameters, including haemodynamics and exercise capacity	Galiè, Nazzareno; Müller, Katharina; Scalise, Andrea-Viviana; Grünig, Ekkehard. PATENT PLUS: a blinded, randomised and extension study of riociguat plus sildenafil in pulmonary arterial hypertension. Eur. Respir. J. 2015;45(5):1314-1322.	rates of discontinuation due to hypotension and three (18%) deaths (not considered study drug-related by the investigator). There were potentially unfavourable safety signals with sildenafil plus riociguat and no evidence of a positive benefit/risk ratio. Concomitant use of riociguat with phosphodiesterase-5 inhibitors is therefore contraindicated	NA	This small RCT noted that the combination of riociguat and sildenafil, compared to sildenafil alone didn't make a difference to the primary outcome (max change in supine SBP 4 hrs post administration) and there were some unfavourable safety signals reported. The authors recommend that concomitant use of riociguat with phosphodiesterase-5 inhibitors is contraindicated.

2-	Cohort	324 (of the 396 patients originally entered into the PATENT1 study)	Riociguat administered in doses that were individually adjusted for each patient up to 2.5 mg three times daily (2.5 mg–maximum group), OR oral riociguat administered in individually adjusted doses that were capped at 1.5 mg three times daily (1.5 mg–maximum group).	Clinical effectiveness of the intervention	Mean 6 minute walking distance	At 1-year time point, mean±sd 6-min walking distance had changed by 51±74 m	WHO functional class	WHO functional class had improved in 33%, stabilised in 61% and worsened in 6% of the patients versus the PATENT-1 baseline	Rubin, Lewis J.; Galiè, Nazzareno; Grimminger, Friedrich; Grünig, Ekkehard; Humbert, Marc; Jing, Zhi-Cheng; Keogh, Anne; Langleben, David; Fritsch, Arno; Menezes, Flavia; Davie, Neil; Ghofrani, Hossein-Ardeschir. Riociguat for the treatment of pulmonary arterial hypertension: a long-term extension study (PATENT-2). Eur. Respir. J. 2015;45(5):1303-1313.	na	na	This was an observational follow up of the PATENT1 cohort of patients with symptomatic PAH (detail re aetiology is defined in the manuscript) with pulmonary vascular resistance greater than 300 dyn · sec · cm–5, a mean pulmonary-artery pressure of at least 25 mm Hg, and a 6-minute walk distance of 150 to 450 m. The study concluded that long-term riociguat was well tolerated in patients with pulmonary arterial hypertension, and led to sustained improvements in exercise capacity and functional capacity for up to 1 year. The risk of bias given the manufacturer involvement that was noted in the appraisal of the original paper remains. This should be seen as a study reporting on the active riociguat arm. Again, the clinical significance of the 6mWD finding may be considered further.

1-	Other	443	Riociguat administered in doses that were individually adjusted for each patient up to 2.5 mg three times daily (2.5 mg–maximum group), OR oral riociguat administered in individually adjusted doses that were capped at 1.5 mg three times daily (1.5 mg–maximum group).	Clinical effectiveness of the intervention compared to existing interventions	Change from baseline at Week 12 in 6MWD	In the riociguat group, 49% of treatment-naïve patients and 37% of patients on background PAH-targeted therapy achieved an increase in 6MWD of ≥40 m at Week 12 compared with 20% and 27% of placebo-treated patients	Change from baseline at Week 12 in PVR, NT-proBNP levels, and WHO Functional Class	In the riociguat group, there was an increase in the proportion of treatment-naïve patients (+12%) and patients on background PAH-targeted therapy (+19%) achieving WHO FC I/II at Week 12, whereas in the placebo group, there was little or no improvement from baseline in either sub-group (0% and +5%, respectively). In the riociguat group, 72% of treatment-naïve patients and 81% of patients on background PAH-targeted therapy (+30% and +33%, respectively) achieved a cardiac index of ≥2.5 liter/min/m2 at Week 12 compared with 42% and 47% of placebo-treated patients (−2% and −6%, respectively). The proportion of treatment-naïve patients (+17%) and patients on background PAH-targeted therapy (+18%) with SvO2 ≥ 65% was increased in the riociguat group, whereas treatment with placebo resulted in a notable decrease in both sub-groups at Week 12 (both −14%). In general, there was a small increase in the proportion of riociguat-treated patients achieving RAP < 8 mm Hg and a small decrease in the proportion of placebo-treated patients achieving this threshold in both sub-groups at Week 12. There was a trend toward an increase in the proportion of riociguat-treated patients achieving NT-proBNP < 1,800 pg/ml in both sub-groups and a small decrease in the proportion of placebo-treated patients achieving this threshold at Week 12.	Langleben, David; Galiè, Nazzareno; He, Jianguo; Huang, Yigao; Humbert, Marc; Keogh, Anne; Rubin, Lewis J.; Zhou, Daxin; Curram, John; Davie, Neil; Ghofrani, Hossein-Ardeschir. Use of clinically relevant responder threshold criteria to evaluate the response to treatment in the phase III PATENT-1 study. J. Heart Lung Transplant. 2015;34(3):338-347.	na	Overall - the proportion of patients with a combination of response criteria (6MWD ≥ 380 m, WHO FC I/II, cardiac index ≥2.5 liter/min/m2, NT-proBNP < 1,800 pg/ml, and SvO2 ≥65%) was 15% and 13% at baseline in the riociguat group (n = 193) and the placebo group (n = 93), respectively. After 12 weeks of treatment, the proportion increased to 34% in the riociguat group, whereas it was largely unchanged in the placebo group (16%).	In summary this reported data from the PATENT1 cohort reports that at 12 weeks the proportion of patients in the riociguat treated group achieving combined response criteria is 34%, compared to 16% in the placebo group; the baseline characteristics are similar.

N/a	Other	Hypothetical population of 1 million	N/A - dosages and specific regime not documented	Other	N/a	N/a	N/a	N/a	Burudpakdee, Chakkarin; Shah, Anshul; Joish, Vijay N.; Divers, Christine; Yaldo, Avin. Budgetary Impact of Adding Riociguat to a US Health Plan for the Treatment of Patients with Pulmonary Arterial Hypertension or Chronic Thromboembolic Pulmonary Hypertension. Am Health Drug Benefits 2014;7(9):479-487.	N/a	N/a	This study reported the Budgetary Impact of Adding Riociguat to a hypothetical US population of 1 million for the treatment of patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. The model estimated that the incremental per capita costs for coverage for riociguat were $0.27 in a medicare insured population. As this was a US study some caution should be exercised in extrapolating this study to England.
N/a	Other	na	na	Clinical effectiveness of the intervention compared to existing interventions	N/a	N/a	N/a	N/a	Khaybullina, Diana; Patel, Ami; Zerilli, Tina. Riociguat (adempas): a novel agent for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. EHJ October 2015 2014;Riociguat (adempas): a novel agent for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.	N/a	N/a	This is the ESC / ERS clinical guideline on the diagnosis and management of PH. As such it has considered the evidence already identified in this review, no additional studies were highlighted in the ESC/ERS guideline. The guideline correctly identifies the main RCTs and extension studies for this drug / indication - Ghofrani (2013) and Galie (2015). Riociguat is recommended both as monotherapy for PAH (Group 1) and sequential combination therapy (in combination with Bosentan). The combination with PDE-5i is contraindicated. No specific recomendation is made in patients with left heart disease. In patients with CTEPH, Riociguat is recommended in symptomatic patients who have been classified as having persistent/recurrent CTEPH after surgical treatment or inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon. This recommendation is made on the basis of the Ghofrani et al (2013) study.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	ERS/ESC guidelines
Updated search terms - Population	Pulmonary Arterial Hypertension Pulmonary Hypertension PAH PH Pulmonary hypertension WHO functional class II or III
Updated search terms - Intervention	Riociguat Adempas soluble guanylate cyclase sGC Riociguat and ERA Riociguat and Prostaglandin
Updated search terms - Comparator	Phosphodiesterase type 5 inhibitor PDE5 Sildenafil Revatio Tadalafil Endothelin receptor antagonist ERA Bosentan Ambrisentan Macitentan Prostaglandins Prostacyclin Epoprostenol Iloprost
Updated search terms - Outcome	N/A

Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, articles will be selected based on the following criteria. 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 reaches 30, inclusion stops here 3.All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	ERS/ESC guidelines to be included at request of PWG
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (where studies with >50 subjects exist) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist)
	Specific exclusion criteria
	N/a