NHS England

Clinical Commissioning Policy Proposition:

Riociguat for Pulmonary Arterial Hypertension

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Clinical Commissioning Policy Proposition: Riociguat for Pulmonary Arterial Hypertension

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Prepared by NHS England Specialised Services Clinical Reference Group for **Pulmonary Hypertension**

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Plain Language Summary

Pulmonary arterial hypertension (PAH), a subcategory of pulmonary hypertension (PH) is a serious condition where the blood pressure in the pulmonary arteries is high. This causes progressive damage to the heart and lungs.

There are many different treatments available for PAH. These treatments can improve the symptoms of PAH and therefore improve quality of life. Some can slow the progression of PAH and can also help reverse damage to the heart and lungs. Treatment for PAH can be split into three categories, conventional therapy, disease-targeted therapy and surgery. Conventional treatments focus on managing the patient's symptoms caused by PAH (for example by reducing excess fluid) whilst disease-targeted therapies focus on clinical, functional and haemodynamic improvement by acting on the disease pathway itself. Many people with PAH are treated with both conventional and targeted therapies, although this can be different for different people. Surgey is beneficial in some cases of PH but not PAH. How PAH is treated will depend on a number of things, for example how severe the PAH is or what type of PAH the patient has.

This policy concerns the use of one of those disease-targeted therapies, riociguat, for adult patients with pulmonary hypertension. NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of riociguat for pulmonary arterial hypertension only for the specific patient population identified in this policy.

1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission riociguat for specific patients with pulmonary arterial hypertension.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether riociguat for pulmonary arterial hypertension will be routinely commissioned is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

2. The proposed intervention and clinical indication

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.

3. Definitions

PAH is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest (assessed by right heart catheterisation), a pulmonary wedge pressure of ≤15 mmHg and a pulmonary vascular resistance ≥3 Wood units.

PH can be classified based on the aetiology:

1. Pulmonary arterial hypertension
    1.1 Idiopathic PAH
    1.2 Heritable PAH 1.2.1 BMPR2 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3 1.2.3 Unknown
    1.3 Drug and toxin induced
    1.4 Associated with: 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart diseases 1.4.5 Schistosomiasis 1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis′ 1" Persistent pulmonary hypertension of the newborn (PPHN).

2. Pulmonary hypertension due to left heart disease
    2.1 Left ventricular systolic dysfunction
    2.2 Left ventricular diastolic dysfunction
    2.3 Valvular disease
    2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies.

3. Pulmonary hypertension due to lung diseases and/or hypoxia
    3.1 Chronic obstructive pulmonary disease
    3.2 Interstitial lung disease
    3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
    3.4 Sleep-disordered breathing
    3.5 Alveolar hypoventilation disorders
    3.6 Chronic exposure to high altitude
    3.7 Developmental lung diseases.

4. Chronic thromboembolic pulmonary hypertension (CTEPH) - riociguat is already commissioned for this indication

5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH.

The WHO provides a functional assessment grading for the severity of PH:

Class I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or syncope.
Class II: Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
Class III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
Class IV: Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may be present even at rest. Discomfort is increased by any physical activity.

This policy only conerns the use of riociguat for the above indications 1 - 1.4.5 and patients in WHO functional class II or III only.

4. Aim and objectives

This policy proposition aims to define NHS England's commissioning position on riociguat as a monotherapy or in combination with other PAH therapies as part of the treatment pathway for adults with WHO functional class II or III PAH of aetiologies 1 - 1.4.5 (as per Section 3).

The objective is to ensure evidence based commissioning with the aim of improving outcomes for adults with WHO functional class II or III PAH of aetiologies 1 - 1.4.5 (as per Section 3).

5. Epidemiology and needs assessment

The estimated annual incidence of diagnosed PAH in the general population ranges from 0.9 to 7.6 cases per million persons, while the prevalence of diagnosed PAH in the general population is between 6.6 and 26 cases per million persons (Frost et al., 2013, Peacock et al., 2007). Incidence and prevalence rates may be underestimated as a result of incorrectly and/or undiagnosed patients.

Between March 2013 and April 2014, 8,431 patients were treated by the UK pulmonary hypertension services, of which 45% (3,794) have the diagnosis of pulmonary arterial

hypertension (diagnoses 1 - 1.4.5 in section 3). Over the same period, 49% (4,103) of patients received disease-targeted drug therapy, of which 81% (3,323) received sildenafil. This policy does not seek to commission riociguat as a competitor to sildenafil for these patients, rather as a substitute when already commissioned therapies are failing to achieve stasis in disease progression. Of the patients with pulmonary arterial hypertension started on monotherapy, 65% will experience failure of the monotherapy within two years (National Pulmonary Hypertension Audit, 2014)

Clinicians have estimated that there are approximately 300 patients expected to be suitable for riociguat therapy based upon the criteria for commissioning in Section 7. According to these criteria, there are three distinct groups of patients where riociguat therapy would be commissioned as a substitute to first line therapies.
(1) For patients in functional class II or III, as a monotherapy for those contraindicated or intolerant of a PDE5 inhibitor, c.20-30 patients.
(2) For patients in functional class III, as dual therapy in combination with an ERA, c. 150-200 patients.
(3) For patients in functional class III, as dual therapy in combination with a prostaglandin, where a PDE5 inhibitor is contraindicated or not tolerated, c.25-50 patients.

6. Evidence base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of riociguat for pulmonary arterial hypertension in specific patient groups. It should be noted that within this field, all major randomised trials are, and will continue, to be sponsored by the pharmaceutical industry. In addition, due to the progressive nature of PAH, head to head comparator trials are unlikely to be carried out as the common clinical practice in other countries is to add medications in combination, rather than to trial monotherapies. The largest trial to date concerning PAH involves 1,154 patients across three continents; the number of patients needed to carry out a non-inferiority study would be greater than three times this amount.

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.

7. Proposed criteria for commissioning

In addition to the patient population and disease-targeted treatments commissioned in the NHS England commissioning policy A11/P/c, riociguat will be routinely commissioned for patients who meet the following criteria (refer to diagram in conjunction with the critera):

(1) Confirmed diagnosis of pulmonary arterial hypertension assessed to be in WHO functional class II or III

AND

(2) Belonging to one of the following clinical classifications:
1. Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug and toxin induced
1.4 Associated with: 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart diseases 1.4.5 Schistosomiasis 1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis′

For these patients, riociguat will be commissioned as:

(1) As an alternative monotherapy for functional class II or III patients where a PDE5 inhibitor is contraindicated (due to intolerance or adverse drug reaction), as an alternative to an ERA.

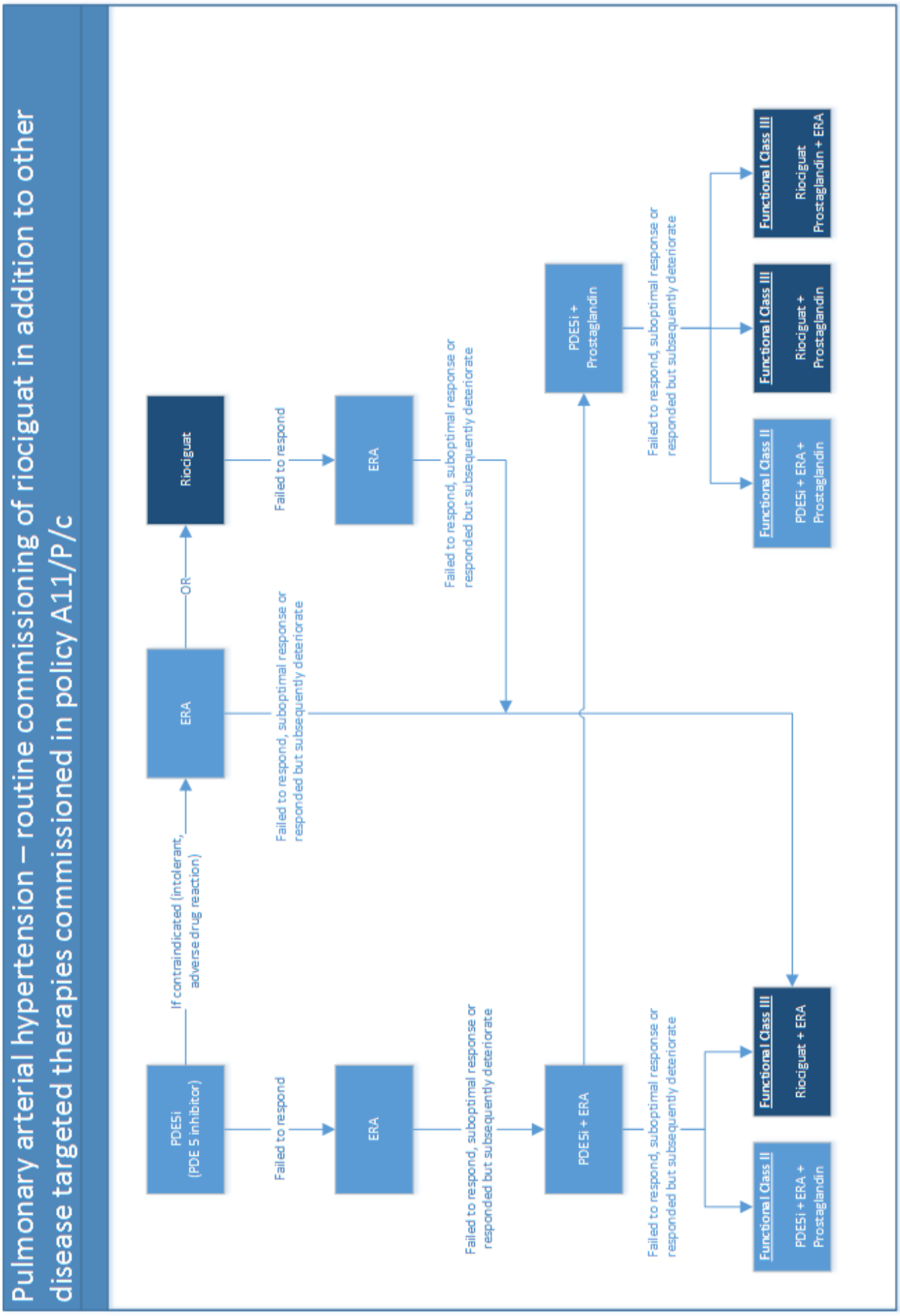
OR

(2) As a third-line therapy (see pathway), in combination with an ERA for functional class III patients, as an alternative to the combination of a PDE5 inhibitor, an ERA and a prostaglandin.

OR

(3) As a third-line therapy (see pathway), either in combination with a prostaglandin or in combination with an ERA and prostaglandin, for functional class III patients, as an alternative to the combination of a PDE5 inhibitor, an ERA and a prostaglandin.

Riociguat will not be routinely commissioned:
(1) For any patients outside of the described clinical classification
(2) For use in any other treatment combinations
(3) For use in patients receving a PDE5 inhibitor or nitrate medictions
(4) For use in pateints who display adverse drug reactions to riociguat


Pulmonary arterial hypertension – routine commissioning of riociguat in addition to other disease targeted therapies commissioned in policy A11/P/c
PDE5i (PDE 5 inhibitor)
If contraindicated (intolerant, adverse drug reaction)
ERA
OR
Riociguat
Failed to respond
ERA
Failed to respond, suboptimal response or responded but subsequently deteriorate
PDE5i + ERA
Failed to respond, suboptimal response or responded but subsequently deteriorate
PDE5i + Prostaglandin
Failed to respond, suboptimal response or responded but subsequently deteriorate
Functional Class III
Riociguat + ERA
Functional Class II
PDE5i + ERA + Prostaglandin
Functional Class III
Riociguat + Prostaglandin
Functional Class III
Riociguat Prostaglandin + ERA

8. Proposed patient pathway

All patients with PAH will receive structured care and follow up as recommended by the ERS/ESC guidelines. As appropriate, disease targeted therapy will be initiated and escalated in accordance with the NHS commissioning policy for England.

The service for patients with suspected pulmonary hypertension comprises the following elements:

Referral:

The predominant symptom of PAH is dyspnoea on exertion, and most patients present with this symptom. Approximately one-third of PAH patients also experience angina during the course of the disease, and syncope occurs in a similar proportion of patients. Patients with PAH are prone to contract pneumonia, the cause of death in 7% of cases. With progression to decompensated right heart failure, patients develop fluid retention that leads to increased central venous pressure, abdominal organ (e.g. hepatic) congestion, peripheral oedema and ascites.

Referral to PH service from consultant physician (typically cardiology or respiratory but also from other services including haematology, rheumatology, infectious disease) for patients where PAH is suspected as a cause of symptoms.

Occasionally, a patient may require urgent referral following a telephone conversation. This may require the patient to be admitted to the PH centre from home or from another hospital. Otherwise, an outpatient or day case review will be arranged for the next available clinic. If PH is suspected, a day case or outpatient appointment is required to include clinical examination and history, blood tests, simple imaging, exercise test, electrocardiogram, echocardiogram, simple lung function. All patients referred urgently will be able to see a specialist within two weeks of the PH centre receiving their referral and those who are severely symptomatic will be seen as soon as possible.

Those with unexplained pulmonary hypertension, who are critically sick and clinically appropriate for therapy, will have a bed made available at the designated PH centre and the referring hospital will be offered the bed within 72 hours of the accepting clinician receiving all necessary and appropriate information about the patient. Those with known pulmonary hypertension, where clinically appropriate, will have a bed made available at the PH centre and the referring hospital will be offered the bed within five days of the accepting clinician receiving all necessary and appropriate information about the patient.

Investigations:

If other causes for symptoms cannot be identified, the patient will need confirmation of PAH by right heart catheterisation with vasodilator testing when appropriate and full diagnostic work up. This will require admission to hospital. Diagnostic work includes more complex studies such as computerized tomography, magnetic resonance imaging, perfusion scanning, complex lung function, cardiopulmonary exercise testing, and second line blood tests.

All new patients will complete all investigations required to make a diagnosis and to determine a treatment plan and commence drug therapy within twelve weeks of the referral being received by the designated PH centre. Evidence shows that waiting beyond twelve weeks can compromise survival.

Diagnosis:

Multi-disciplinary team discussion of data takes place for each patient and development of an individualised management plan. Where possible a member of the multi-disciplinary team (e.g. specialist nurse, trained counsellor or social worker) will be present with the patient when the final diagnosis is discussed. The full diagnosis will be communicated to the referring consultant(s) and the GP within 5 working days of the diagnosis and treatment plan being made.

Treatment:

If appropriate, disease-targeted therapy will only be initiated by the PH centre, which is responsible for monitoring and ensuring the safe, long-term prescribing of continuing treatments, where required. Typically, any new therapy or change in regimen is reviewed at three months and then, every three to six months as an outpatient.

Disease-targeted therapy will be prescribed as follows:

First-line therapy:

Disease-targeted therapy will commence with a PDE5 inhibitor (sildenafil or tadalafil) if clinically appropriate. Only if this is contraindicated will an sGCS (riociguat) or an ERA (bosentan, ambrisentan or macitentan) be substituted.

Second-line monotherapy:

Patients who have failed to respond to a trial of therapy of adequate dose and duration (typically eight to twelve weeks), or patients who have failed to tolerate one of the oral first-line therapies will be switched to an ERA as alternative monotherapy.

Patients who have had a suboptimal response to first-line monotherapy, or initially responded to first-line monotherapy but have since deteriorated will be considered for dual therapy.

Second-line dual therapy:

Dual therapy consists of a PDE5 inhibitor and an ERA (bosentan, ambrisentan or macitentan). Patients who display a suboptimal response to dual therapy will be considered for triple therapy.

Third-line combination therapy:

Patients in functional class III who have not achieved stasis of disease progression with a PDE5 inhibitor and an ERA will be switched to riociguat and an ERA. Patients in functional

class II who have not achieved stasis of disease progression with a PDE5 inhibitor and an ERA will have a prostaglandin added to this combination.

In addition, patients in functional class III receiving a PDE5 inhibitor in combination with a prostaglandin who fail to stabilise, will receive riociguat in combination with a prostaglandin or in combination with an ERA and a prostaglandin. Patients in functional class II receiving a PDE5 inhibitor in combination with a prostaglandin who fail to stabilise, will have an ERA added to this combination.

Riociguat will be commenced at an initial dose of 1mg, as per EMA license EMA/51814/2014, three times daily, and up-titrated by the patient (at home) using systemic blood pressure as the measure of effectiveness and in close communication with the PAH team. In addition, patients considered for riociguat therapy will be strongly encouraged to engage with smoking cessation programmes as the evidence demonstrates smoking to impair the benefit of riociguat.

The supportive care needs of all patients on disease targeted therapy will be assessed, taking into account any requirements for home care delivery and support.

For those patients who are eligible for lung transplantation, referral will be sent, using the nationally agreed proforma, to the lung transplant centre within five working days of the clinician's decision.

Follow-up and discharge from specialised service:

The focus of ongoing management by the PH centre is the need for disease targeted therapy; patients who do not have PH or who are not likely to require targeted therapy will be referred back to their referring consultant and CCG funded care. Patients treated with disease targeted therapy will have lifelong follow up within the PH service. The PH centre will identify those patients suitable for shared care and ensure effective communication with shared care centres to plan patient reviews. All such patients will be reviewed at least once each year by the visiting PH specialist or at the PH centre.

9. Proposed governance arrangements

Six centres are designated to provide pulmonary hypertension services for adults. The centres offer investigation and treatment of patients with idiopathic pulmonary hypertension, pulmonary hypertension complicating other diseases and assessment of response to treatment. The centres and staff also provide support for patients and their families.

Only the designated centres are able to initiate treatment with a disease-targeted medicine under this policy.

In some circumstances, explicit and formalised shared-care agreements may be made by the designated centres with other specialist centres to prescribe disease-targeted therapies. However, non-specialist clinicians and general practitioners will not be asked to routinely prescribe these medicines since they are not able to submit information to the

national database.

Where a patient is started on a disease-targeted therapy, their GP will be informed and alerted to any potential for unwanted effects, including interactions with other medicines.

A service specification for pulmonary hypertension has been published by NHS England including standards for the delivery of care.

10. Proposed mechanism for funding

All disease-targeted therapies (including riociguat) will be commissioned by NHS England through local specialised commissioning teams.

11. Proposed audit requirements

Each centre will need to provide commissioners with a monthly monitoring statement covering the following fields:

- ID number
- Patient Initials
- NHS number
- PCT/SCG codes
- Drug and dose
- Notification of changes to drugs and dosage
- Discontinuation date
- Reason for discontinuation
- Monthly cost
- Annual cost
- Survival
- Quality of Life estimate (emphasis 10)
- Absolute 6 minute walk

The above data will need to be submitted to the National Pulmonary Hypertension Audit.

12. Documents which have informed this policy proposition

Clinical Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults (Reference NHS England A11/P/c)

13. Date of review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by June 2016).