



Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults

Reference: NHS England A11/P/c

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Description	NHS England will routinely commission this specialised treatment in accordance with the criteria described in this policy.
Cross Reference	
Superseded Docs (if applicable)	
Action Required	
Timing / Deadlines (if applicable)	
Contact Details for further information	ENGLAND.CET@nhs.net for policy issues

Document Status

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1 Executive Summary

Policy Statement

NHS England will commission the treatments outlined in this policy in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

NHS England has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which NHS England is responsible, including policy development, review and implementation.

Plain Language Summary

Pulmonary hypertension (often shortened to 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 PH. These treatments can improve the symptoms of PH and therefore improve quality of life. Some can slow the progression of PH and can also help reverse damage to the heart and lungs.

Treatment for PH can be split into three categories, conventional therapy such as diuretics, targeted therapy and surgery. Many people with PH are treated with both conventional and targeted therapies, although this can be different for different people. Some people with PH may need surgery. How PH is treated will depend on a number of things, for example how severe the PH is or what type of PH the patient has.

This policy describes the use of targeted therapies for adult patients with pulmonary hypertension currently funded by NHS England.

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 (Galiè N et al., 2009). This results in a progressive increase in pulmonary vascular resistance (PVR) which can ultimately lead to right heart failure and premature death (Galiè N et al., 2009). PAH is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg (assessed by right heart catheterization [RHC]), a pulmonary wedge pressure of ≤ 15 mmHg and normal or reduced cardiac output (Galiè N et al., 2009).

PAH can be classified into five etiological subgroups including; idiopathic, heritable, drug and toxin induced, associated, and persistent pulmonary hypertension of the newborn (Simonneau et al., 2009). 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 (FC) (Rubin, 2004). 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 (Table 1).

There is currently no cure for PAH, other than lung transplantation (Galiè N et al., 2009).

Updated Classification of Pulmonary Hypertension*

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 Schistosomiasis¹ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis¹". 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)
5. Pulmonary hypertension with unclear multifactorial mechanisms 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangiomyomatosis 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH.

Taken from Simonneau G et al (2013).

2 Definitions

Pulmonary hypertension (PH) is a rare disorder of the blood vessels in the lung,

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characterised by raised pressure in the pulmonary artery, which results in a range of symptoms and may be life threatening.

PH is defined as an increase in mean pulmonary artery pressure (PAP) of 25mmHg or greater at rest as assessed by right heart catheterisation. A definition of PH on exercise (as a mean PAP >30mm Hg) is not supported by published data.

PH can be found in a diverse range of clinical conditions, including connective tissue disease, congenital heart diseases, chronic pulmonary thromboembolism, sickle cell disease, HIV infection, use of an appetite suppressant, and liver disease.

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.

Chronic thromboembolic pulmonary hypertension (CTEPH), is a form of pulmonary hypertension (PH), categorized by the WHO as Group 4 PH.

It is defined as mean pulmonary arterial pressure ≥ 25 mmHg and pulmonary capillary wedge pressure ≤ 15 mmHg in the presence of multiple chronic/organized occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, sub-segmental) after at least three months of effective anticoagulation.

Functional class

Assessment of WHO Functional Class (FC) is an important predictor of survival, despite large inter-observer variation in its measurement. Table 2 describes the characteristics of the four classes.

In untreated patients with IPAH or heritable PAH, historical data suggests a median survival of 6 months in patients in WHO-FC IV, 2.5 years for those in WHO-FC III, and 6 years for WHO-FC I and II.¹

It is expected that defining a patient's functional class will be a multidisciplinary team decision.

Table 2: Functional classification of PH¹	
Class I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope.
Class II	Patients with pulmonary hypertension 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 pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea, fatigue, and chest pain or near syncope.
Class IV	Patients with pulmonary hypertension 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.

3 Aims and Objectives

This policy aims to provide criteria against which treatments for PAH and CTEPH will be commissioned. In addition, it includes the inclusion of a new class of drug riociguat which is a soluble guanylate cyclase stimulator.

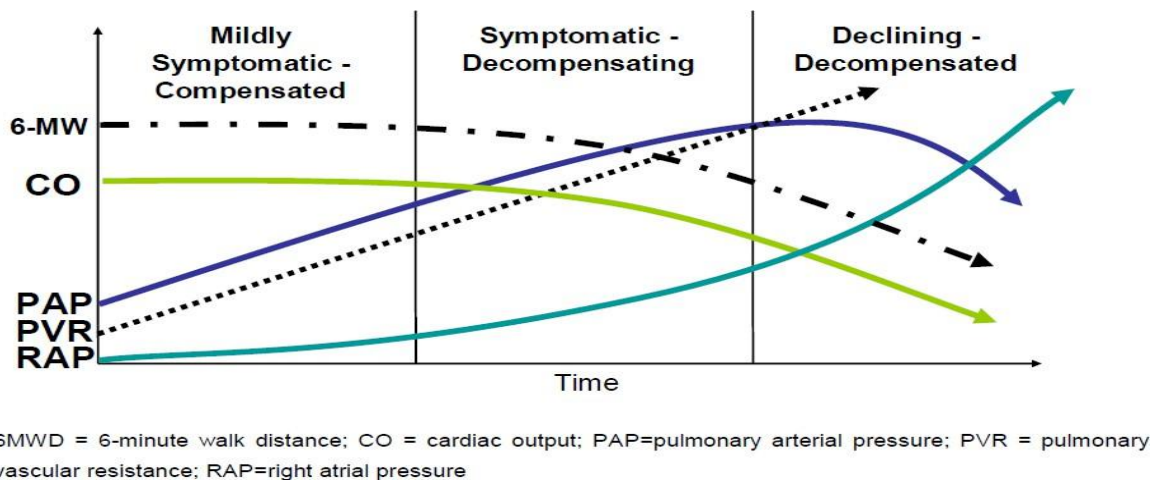
This amendment relates only to the use of subcutaneous or intravenous treprostinil for the specified indication. All other policy recommendations remain unchanged at this time.

4 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, Humbert et al., 2006, Peacock et al., 2007, Ling et al., 2012, Hurdman et al., 2012). Incidence and prevalence rates may be underestimated as a result of mis and/or undiagnosed patients (Frost et al., 2013).

Natural history

PAH is a progressive illness; if not diagnosed early and/or left untreated, patient condition can deteriorate rapidly, leading to premature mortality in all aetiologies (Gomberg-Maitland, 2011). Figure 1 below demonstrates the progression of PAH over time, as measured by hemodynamic parameters (ref adapted from Harrison's Principles of Internal Medicine, 14th ed).



As shown, the disease can progress even while the patient remains asymptomatic or exhibits only non-specific and subtle signs of PAH. In addition, mildly symptomatic patients may already have impaired hemodynamics, including elevated PVR and pulmonary arterial pressure (PAP).

The predominant symptom of PAH is dyspnoea on exertion, and most patients present with this symptom (Galiè N et al., 2009, McLaughlin et al., 2009b, McGoon and Kane, 2009). Approximately one-third of PAH patients also experience angina during the course of the disease, and syncope occurs in a similar proportion of patients (McGoon and Kane, 2009). Patients with PAH are prone to contract pneumonia, the cause of death in 7% of cases (Galiè N et al., 2009). 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 (Galiè N et al., 2009); (McGoon and Kane, 2009).

5 Evidence Base

The evidence for PAH treatments approved before April 2013 were reviewed by the former Yorkshire and Humber Specialised Commissioning Group (SCG) on behalf of the ten former SCGs in England. This review supported the approval of the National PAH Guidelines published in 2011 and subsequent adoption by NHS England as a policy statement. The policy was further amended to include the addition of macitentan, a new endothelin receptor antagonist in May 2014. In 2015, this policy was updated to include the addition of riociguat, a new drug from a class of treatments termed “Soluble Guanylate Cyclase Stimulators (SGCS)” therapies for approval within the policy for the treatment of patients with Chronic Thromboembolic Pulmonary Hypertension (CTEPH).

Macitentan is a dual endothelin A/B (ET_A/ET_B) receptor antagonist.(Iglarz et al., 2008) It is fundamentally different from the other ERAs currently approved for PAH therapy – namely, the dual ET_A/ET_B receptor antagonist, bosentan, and the ET_A-selective antagonist, ambrisentan.(Bolli et al, 2012)

Clinical efficacy has been documented in one randomised, double-blind, placebo-controlled Phase III trial (Pulido et al., 2013). This study (SERAPHIN) is the largest and longest randomised trial conducted to date in PAH, using the recommended primary outcome of morbidity and mortality (McLaughlin et al., 2009c). Existing oral PAH therapies have been approved on the basis of small, randomised clinical trials with short follow-up periods and with primary outcomes that do not reflect clinical events indicative of true disease progression.

Macitentan is the first PAH-specific agent shown to have an impact on clinical outcomes in an event-driven, long-term randomised controlled trial (RCT).

SERAPHIN demonstrated a significant and clinically relevant 45% reduction in the risk of morbidity and mortality outcomes with macitentan versus placebo (p<0.001). This effect was established early and sustained over a median treatment duration of

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more than two years. Importantly, macitentan significantly reduced the risk of morbidity and mortality in patients treated with PAH-specific background therapy, consisting mainly (96%) of phosphodiesterase-5 (PDE-5) inhibitors (38% reduction, $p=0.009$), as well as in treatment-naïve patients. A significant reduction was also demonstrated in the risk of death or hospitalisation due to PAH (50%, $p<0.001$), as well as the frequency of (55%, $p<0.001$) and length of stay for PAH-related hospitalisations (52% reduction, $p=0.04$) (Actelion Pharmaceuticals Ltd, 2012).

In addition, treatment with macitentan led to improvements in short-term endpoints, including six-minute walk distance (6MWD) and WHO FC (Pulido et al., 2013).

Treatment with macitentan also showed significant and clinically relevant improvements in health-related quality of life (HRQoL) assessed using the short form 36 (SF-36) questionnaire. While it is not possible to compare the risk of morbidity and mortality between macitentan and other endothelin receptor antagonists (ERAs), a comparison based on short-term endpoints showed no significant differences.

Changes in short-term endpoints are, however, not predictive of long-term outcomes. Therefore, macitentan is the only ERA which has demonstrated both short- and long-term benefits in an RCT. Consequently, macitentan is the only PAH-specific therapy with a licence for long-term treatment.

Treatment with macitentan was well tolerated, with a similar overall incidence of treatment-emergent adverse events (TEAEs) to placebo. The majority of AEs in the trial were mild-to-moderate in intensity, with nasopharyngitis, headache and anaemia being reported most frequently. A significant safety concern associated with ERAs has been their potential for causing liver injury. The incidence of liver disorders and abnormal liver function-related AEs with macitentan was similar to that observed with placebo, as was the risk of oedema (Pulido et al., 2013).

Riociguat: the evidence for riociguat for the treatment of inoperable/residual CTEPH, data was gathered from published literature. Articles were retrieved by electronic search strategy. Searches were carried out in MEDLINE, Cochrane, NHS Evidence and CRD databases. The search terms used were 'Riociguat', 'Adempas', 'Sildenafil', 'Viagra', 'Tadalafil', 'Cialis', 'Pulmonary hypertension', 'Pulmonary arterial

hypertension', 'Chronic thromboembolic pulmonary hypertension' and their combinations.

Inclusion criteria

- Articles published between January 2000 and July 2014
- Articles in the English language
- Phase 3 Randomised control trials reporting clinical efficacy and safety
- Any study designs reporting on cost-effectiveness

One study was found which met the inclusion criteria, reporting on the clinical effectiveness and safety of Riociguat for CTEPH- see Table 1.

Table 1: Riociguat for CTEPH

Study type	Reference
RCT	Ghofrani et al 2013b

Clinical Effectiveness of Riociguat in treatment of inoperable/residual CTEPH

A phase 3 multi centre, double blinded RCT which included 261 patients chronic thromboembolic pulmonary hypertension that was adjudicated to be technically inoperable (72%) or if they had persistent or recurrent pulmonary hypertension after undergoing pulmonary endarterectomy (28%) and if they had:

- a pulmonary vascular resistance greater than $300 \text{ dyn} \cdot \text{sec} \cdot \text{cm}^{-5}$,
- a mean pulmonary-artery pressure of at least 25 mm Hg, and
- a 6 minute walk distance (MWD) of 150 to 450 m.

Patients were excluded if they had received an endothelin-receptor antagonist, prostacyclin analogue, PDE5i, or nitric oxide donor within the 3 months before study entry. Majority of patients were in WHO functional class II or III (31% and 64% respectively). 72% of patients had inoperable chronic thromboembolic pulmonary hypertension whilst (28%) had postoperative persistent or recurrent pulmonary hypertension. Majority of patients were in WHO functional class II or III (31% and 64% respectively). Patients received placebo or individually adjusted to a maximum of 2.5 mg Riociguat 3 times daily

At 16 weeks, the primary end point of 6MWD, in the Riociguat group was reported to be increased by 39 m compared with a 6 m decrease in the placebo group ($p < 0.001$) from a baseline of 342 m, mean difference of 46 m; 95% confidence interval [CI], 25 to 67; $P < 0.001$). This effect was seen in both patients with inoperable and residual CTEPH post-PEA although a greater increase was seen in the inoperable group (54 vs 26 m). Increases in primary outcome reported (mean ($\pm$ SD) an increase of 63 ± 64 m over the baseline distance in CHEST-1 during the first 12 weeks of the long-term extension study (CHEST-II, $n=129$).

Riociguat was also associated with significant improvements in the secondary endpoints of PVR, NTproBNP and WHO functional class at 16 weeks.

Safety of Riociguat in treatment of inoperable/residual CTEPH

Overall, riociguat was well tolerated in the CHEST- I study. 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%). A case of acute renal failure was considered by the investigator to be related to the study drug.

Cost Effectiveness of Riociguat in treatment of inoperable/residual CTEPH

No cost effectiveness studies related to use of Riociguat in CTEPH were found.

Clinical Effectiveness of Riociguat in treatment of potentially operable CTEPH

No studies related to use of Riociguat in potentially operable CTEPH were found.

Safety of Riociguat in treatment of potentially operable CTEPH

No studies related to use of Riociguat in potentially operable CTEPH were found.

6 Rationale behind the Policy Statement

This policy updates the existing NHS England clinical commissioning policy A11/P/b to include subcutaneous or intravenous treprostinil as a treatment option for patients with PAH.

7 Criteria for Commissioning

This policy has been agreed on the basis of NHS England's understanding of the likely price of care associated with enacting the policy for all patients for whom NHS England has funding responsibility, as at the time of the policy's adoption. Should these prices materially change, and in particular should they increase, NHS England may need to review whether the policy remains affordable and may need to make revisions to the published policy.

Included patient populations

Treatment with disease-targeted medicines will be routinely commissioned for adults, assessed as in WHO-FC III or IV, in one of the following clinical classifications:

- Group 1 Pulmonary arterial hypertension (PAH)
- Group 1* Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary haemangiomatosis (PCH)
- Group 4 Inoperable chronic thromboembolic pulmonary hypertension
- (CTEPH) [NB This includes patients with potentially operable disease who refuse surgery or who are waiting for acceptance for surgery]

Treatment will also be routinely commissioned for patients with chronic renal failure on dialysis or sarcoidosis associated with pulmonary hypertension, and for women who are pregnant (see below), who fall within one of the allowed classes described above.

Excluded patient populations

Treatment with disease-targeted medicines will not be routinely commissioned for patients in the following groups unless described otherwise above:

- WHO-FC I or II (except for those patients who meet the clinical criteria listed in the Clinical Commissioning Policy A11/P/a: Targeted Therapies for Pulmonary Hypertension Functional Class II).
- Patients in clinical classifications 2 and 3 (Table 2): the use of targeted therapies for patients in these classifications is not recommended until robust data are available.
- PH with unclear or multifactorial mechanisms (clinical classification group 5): there is no robust evidence to support treatment with targeted therapies in these patient groups. NB: treatment for patients with chronic renal impairment on dialysis and those with sarcoidosis is routinely commissioned.

1.1 Approved medicines

Four types of medicine may be used under this policy. However, due to differences between some products within each class, particularly in price, they are commissioned by individual product rather than by type, unless stated otherwise.

Doses above those specified (e.g. bosentan 250mg twice daily) will not be routinely funded.

1) Phosphodiesterase type 5 inhibitors (PDE5I)

a) Sildenafil (oral)

- As generic sildenafil tablets (unlicensed indication): for dose escalation 25-100mg three times daily
- As Revatio tablets: for use only at licensed dose of 20mg three times daily

b) Tadalafil (oral) tablets: for use only at licensed dose of 40mg once daily

2) Endothelin receptor antagonists (ERA) (NB commissioned by type)

a) Bosentan (oral) tablets: 62.5mg – 125mg twice daily

b) Ambrisentan (oral) tablets: 5-10mg once daily

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c) Macitentan* (oral) tablets: 10mg once daily

*Only when purchased at the commercial in confidence discount

Soluble Guanylate Cyclase Stimulators (SCGS)

a) Riociguat* (oral) tablets: dose as per titration – usually 2.5mg three times daily

*Only when purchased at the commercial in confidence discount

3) Prostanoids

a) Epoprostenol (intravenous): dose titrated to response

b) Iloprost (nebulised): 5micrograms up to 9-times daily

c) Iloprost (intravenous, unlicensed product): dose titrated to response

d) Treprostinil (sub-cutaneous, intravenous): dose titrated to response

In addition to epoprostenol and iloprost, NHS England will routinely commission treprostinil for eligible patients with PAH when prescribed by a designated specialist pulmonary hypertension centre in accordance with this policy. Treprostinil may be administered by sub-cutaneous or intravenous routes in accordance with the Summary of Product Characteristics (SmPC).

Approved regimens – Pulmonary Arterial Hypertension

First line therapy

- Monotherapy with an oral PDE5I will be routinely commissioned as first line therapy.
- Where a PDE5I is not clinically appropriate, an ERA may be substituted.
- The choice of medicine is subject to clinical discretion bearing in mind relative safety, evidence of efficacy, and cost of treatment.
- Monotherapy with a prostanoid will be routinely commissioned for patients at WHO FC-IV with clinical classification 1 or 1* (see table 2).

Second line therapy

- Patients who have failed to respond to a trial of therapy of adequate dose and

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duration (typically 8-12 weeks treatment), or failed to tolerate one of the oral therapies should be switched to an alternative oral product as monotherapy.

- Patients who have initially responded to first-line therapy but then deteriorated despite dose escalation (if appropriate) may be considered for dual therapy (see below).
- Patients who have had a suboptimal response to first-line therapy (with dose escalation where appropriate) may be considered for dual therapy.
- A prostanoid will be routinely commissioned for patients with clinical classification 1 and 1* (see table 2) with WHO FC-III who have failed to respond adequately or tolerate dual therapy with an oral PDE5I and an oral ERA. [NB In exceptional cases, where an acutely unwell patient requires in-patient treatment, monotherapy with a prostanoid may be initiated as an alternative to dual therapy].
- A prostanoid will not be routinely commissioned for use in patients with other clinical classification

Dual therapy

Dual therapy will only be funded in combinations involving a PDE5I unless there are exceptional circumstances.

Dual therapy will be commissioned for patients with progressive disease:

- who have failed to respond to 1st and 2nd-line monotherapy.
- who have initially responded to monotherapy but subsequently deteriorated despite dose escalation (if appropriate).
- who have had a suboptimal response to monotherapy (with dose escalation, where appropriate)

In exceptional cases, where a patient is acutely unwell and hospitalised, the progression to dual therapy may be accelerated.

Triple therapy

Triple therapy will be routinely commissioned only for patients who have been

formally assessed by a transplant centre and accepted as a suitable candidate.

Pregnancy

PH in pregnancy is associated with high mortality. Disease-targeted therapies may be used alone, or in combination, according to clinical signs and symptoms at the discretion of the treating clinician, irrespective of functional class.

Exceptional Cases

Pre-agreed exceptions for dual therapy in combination, not involving a PDE5I, are:

- Dual therapy: as a bridge for a patient switching from one mono-therapy to an alternative mono-therapy (up to a maximum of 12 weeks)
- Dual therapy: for patients who have been listed for the following surgery:
 - Heart-lung transplantation
 - Double Lung transplantation
 - Thrombo-endarterectomy (in patients with chronic thrombo-embolic disease)
- Continuation of existing treatments (including a prostanoid) for patients making the transition from children's services to adult services where it would be inappropriate to change treatments only to comply with the commissioning policy.
- Continuation of existing treatments (including a prostanoid) for adult patients (i.e. started prior to the policy being agreed) which are not in accordance with the commissioning policy is permitted until the patient and their clinician consider it appropriate to stop.

Clinical Trials

NHS England will not pick up the funding of patients exiting clinical trials funded by the pharmaceutical industry, extended access programs or compassionate funding programs unless prior arrangements have been made.

It is seen as the responsibility of those initiating therapy, and manufacturers sponsoring trials, to ensure that there is either an exit strategy or that ongoing treatment is provided. Patients should be fully informed of these arrangements.

Approved regimens – Inoperable / Residual Chronic Thromboembolic Pulmonary Hypertension.

Treatment should be initiated and, where appropriate, escalated with the least expensive suitable product. Doses higher than those specified above will not be routinely funded.

A. Patients with potentially operable CTEPH in WHO FC III or IV.

who have:

- significant RV impairment and/or
- significant comorbidities and/or
- evidence of deterioration whilst awaiting decision for pulmonary endarterectomy

may also be considered for sildenafil. Where sildenafil is not clinically appropriate, tadalafil or an ERA may be substituted.

Triple therapy including riociguat will not be commissioned.

B. Patients in WHO FC II, III or IV unsuitable for surgery either due to comorbidity or patient choice

First line therapy

- Monotherapy with sildenafil will be routinely commissioned. Where sildenafil is not clinically appropriate, an ERA or riociguat may be substituted.

Second line therapy

- Patients who have failed to respond to a trial of therapy of adequate dose and duration (typically 12 weeks treatment), or failed to tolerate one of the oral therapies should be switched to an alternative oral product (riociguat) as monotherapy.
- Operable patients initially declining surgery who fail to respond to medical treatment will be advised to revisit the surgical option.

Dual therapy / Triple therapy

- Dual therapy with addition of ERA or prostanoid to sildenafil will be considered in patients who have failed to respond to a trial of therapy of adequate dose and duration (typically 12 weeks treatment).

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- Dual therapy involving riociguat + ERA or prostanoid will not be commissioned.

Triple therapy will not be routinely commissioned for CTEPH patients. The exception is to consider sildenafil, ERA and a prostanoid but only for patients as listed below:

- Patients with significant inoperable disease felt to be behaving in a similar manner to IPAH
- Patients who have been formally assessed by a transplant centre and accepted as a suitable candidate.

Triple therapy including riociguat will not be commissioned.

C. Patients in WHO FC II, III or IV unsuitable for surgery either due to anatomical distribution of disease or residual CTEPH post PE (The phenotype of patient in the CHEST study)

First line therapy

- Monotherapy with oral riociguat will be routinely commissioned.
- Where riociguat is not appropriate (either clinically or due to titration logistics), sildenafil may be substituted.
- Where both riociguat and sildenafil are not clinically appropriate, tadalafil or an ERA may be substituted.

Second line therapy

- Patients who have failed to respond to a trial of therapy of adequate dose and duration (typically 12 weeks treatment), or failed to tolerate riociguat should be switched to (sildenafil) as monotherapy.

Dual therapy / Triple therapy

- Dual therapy with addition of ERA or prostanoid to sildenafil will be considered in patients who have failed to respond to a trial of therapy of adequate dose and duration (typically 12 weeks treatment).
- Dual therapy involving riociguat + ERA or prostanoid will not be commissioned.

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Triple therapy comprising of sildenafil, + ERA + prostanoid will not be routinely commissioned for CTEPH patients except :

- Patients with significant inoperable disease felt to be behaving in a similar manner to IPAH
- Patients who have been formally assessed by a transplant centre and accepted as a suitable candidate.

Triple therapy including riociguat will not be commissioned.

Pregnancy

CTEPH in pregnancy is associated with high mortality. Disease-targeted therapies may be used alone, in non-operable cases or in combination, according to clinical signs and symptoms at the discretion of the treating clinician, irrespective of functional class, as above. CTEPH is extremely rare in paediatric practice.

Cases not addressed above

Pre-agreed exceptions for dual therapy in combination, not involving sildenafil, are:

- Continuation of existing treatments (including a prostanoid) for patients making the transition from children's services to adult services where it would be inappropriate to change treatments only to comply with the commissioning policy.
- Continuation of existing treatments (including a prostanoid) for adult patients (i.e. started prior to the policy being agreed) which are not in accordance with the commissioning policy is permitted until the patient and their clinician consider it appropriate to stop.

Patient Stopping Criteria

The continued use of target therapies will be reviewed on a regular basis. The key factors influencing the cessation of treatment will be:-

- Successful surgery

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- Clinically relevant side-effects e.g. liver function
- Poor/no response to treatment
- No other active treatment option available

Drug therapies may also be withdrawn “at the end of life” phase.

8 Patient Pathway

Please refer to the service specifications relating to Pulmonary Hypertension Centres (Adult) and Pulmonary Hypertension Shared Care (Adult).

9 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.

Importantly, 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 should 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 should 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.

The designated Adult centres are:

London	Imperial College Healthcare NHS Trust(Hammersmith Hospital)	Cambridge	Papworth Hospital NHS Foundation Trust
	Royal Brompton & Harefield NHS Foundation Trust	Sheffield	Sheffield Teaching Hospitals NHS Foundation Trust (Royal Hallamshire Hospital)
	Royal Free Hampstead NHS Trust	Newcastle	The Newcastle upon Tyne Hospitals NHS Foundation Trust (Freeman Hospital)

NB Great Ormond Street Hospital is a designated “Highly Specialised Service” to provide pulmonary hypertension services for children.

10 Mechanism for Funding

The treatments as defined in this policy are routinely commissioned by NHS England.

11 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
- Takeoff date
- Reason for takeoff
- Monthly cost
- Annual cost
- Survival

- Quality of Life estimate (emphasis 10)
- Absolute 6 minute walk

12 Documents which have informed this Policy

See references

13 Links to other Policies

Clinical Commissioning Policy A11/P/a: Targeted Therapies for Pulmonary Hypertension Functional Class II.

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

14 Date of Review

This policy will be reviewed in October 2017 unless information is received which indicates that the proposed review date should be brought forward or delayed.

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