NHS England

Clinical Commissioning Policy: National policy for targeted therapies for the treatment of pulmonary hypertension in adults May 2014

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Clinical Commissioning Policy: National policy for targeted therapies for the treatment of pulmonary hypertension in adults

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Description	NHS England will commission macitentan as a targetted therapy for the treatment of Pulmonary Hypertension in accordance with the criteria outlined in this document. This policy outlines the arrangements for funding of this treatment for the population in England.
Cross Reference	
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Document Status

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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

Throughout the production of this document, due regard has been given to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited in under the Equality Act 2010) and those who do not share it.

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, what type of PH the patient has, etc.

This policy outlines which targeted therapies are funded by NHS England, including starting and stopping criteria. It builds on the National Guidelines published in 2011 and adopted by NHS England in April 2013. In particular, it includes a new medicine, macitentan.

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.

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

2. Definitions

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.

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.

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 PH[1]

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. Aim and objectives

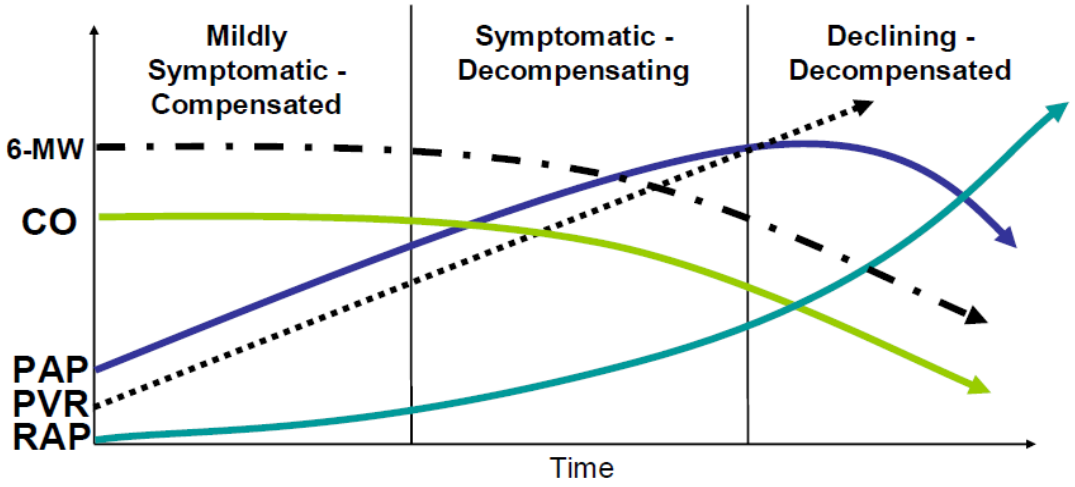
This policy aims to provide criteria against which treatments for PAH will be commissioned. In addition, it includes the inclusion of a new endothelin receptor antagonist, macitentan.

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).



6MWD = 6-minute walk distance; CO = cardiac output; PAP=pulmonary arterial pressure; PVR = pulmonary vascular resistance; RAP=right atrial pressure

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 dyspnea 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 Yorkshire and Humber SCG on behalf of the ten SCG's in England. This review supported the approval of the National PAH Guidelines published in 2011.

This updated policy includes the addition of macitentan, a new endothelin receptor antagonist.

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 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-naive 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).

6. Rationale behind the policy statement

This policy updates the clinical guidelines produced by Yorkshire & Humber SCG to include a new endothelin receptor antagonist, macitentan. This new medicine has shown equal or improved efficacy in treating PAH compared to current endothelin receptor antagonists and is being made available at equivalent costs to other agents through a commercial in confidence discount.

7. Criteria for commissioning

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.

Approved medicines

Three types of medicine may be used under this policy. However, due to differences between some products within each class, particularly in price (see Table 1), 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.

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

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

*Only when purchased at the commercial in confidence discount

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

NB Treprostinil will not be routinely commissioned for new patients but funding will continue for patients already established under the terms of the national policy. Treprostinil is a prostanoid that may be administered by sub-cutaneous or intravenous routes (unlicensed product). While it may have a role in the subcutaneous treatment of very small numbers of seriously ill patients with PH who are not suitable for nebulised or intravenous administration of a prostanoid, commissioners believe that, at around 3-4 times the price of equivalent alternatives, its new pricing structure cannot be justified.

Table 1: Approximate annual treatment costs at recommended doses

	Cost without homecare*
Sildenafil (generic)	£128 - £180
Sildenafil (Revatio)	£5,356
Tadalafil	£6,400
Bosentan	£23,500
Ambrisentan	Circa £23,500
Macitentan (excluding discount)	£27,672
IV Iloprost (including pump)	£39,000
Nebulised Iloprost (Ventafee)	£32,200
Epoprostenol (including pump)	Circa £35,000
Trepostinil (including pump)	Circa £120,000

*Prices will vary depending on local agreements if delivered via homecare

Approved regimens

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.

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

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 accepted as suitable for transplant.

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.

NHS England will fund patients once the service development has been agreed.

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
- 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"

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 centres are:

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

NB: Great Ormond Street Hospital is designated to provide pulmonary hypertension services for children.

10. Mechanism for funding

The treatments listed in this policy are commissioned by NHS England.

It is recommended that PH treatments are funded only within the remit of this policy document

11. Audit requirements

Each centre will need to provide each SCG 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

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 April 2016 unless information is received which indicates that the proposed review date should be brought forward or delayed.

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Change Notice for Published Specifications and Products developed by Clinical Reference Groups (CRG)

Amendment **to the Published Products**

Product Name	Clinical Commissioning Policy-Targeted therapies for the treatment of Pulmonary Hypertension in Adults
Ref No	**A11/P/b**
CRG Lead	Paul Corris

Description of changes required

Describe what was stated in original document	Describe new text in the document	Section/Paragraph to which changes apply	Describe why document change required	Changes made by	Date change made
	Support revision of the Pulmonary Hypertension targeted therapies policy to include the addition of another new drug, Macitentan, within the same class of Endothelin Receptor Antagonists "ERA" therapies approved within the policy.			CRG	March 2014