NHS Commissioning Board

Clinical Commissioning Policy: Targeted Therapies for Pulmonary Hypertension Functional Class II

April 2013

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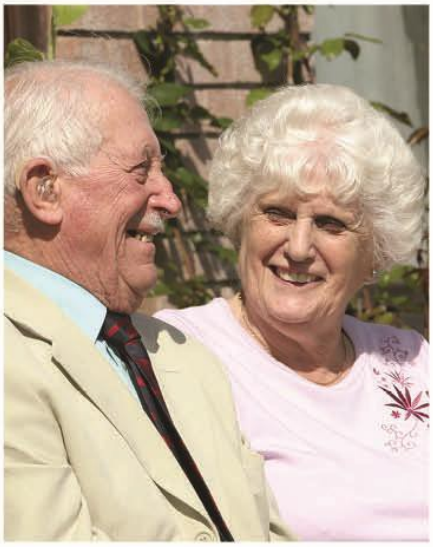

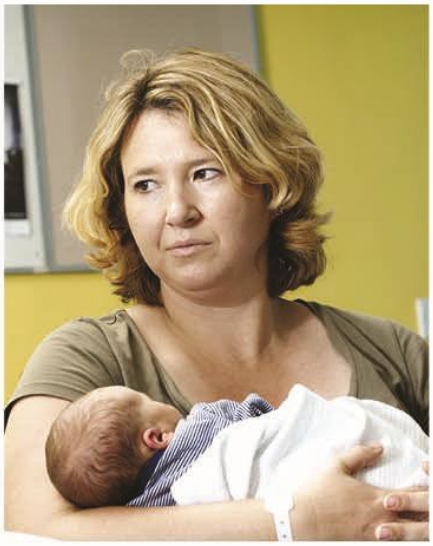

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NHS Commissioning Board

Clinical Commissioning Policy: Amendment to National Policy for Targeted Therapies for the Treatment of Pulmonary Hypertension in Adults to include Functional Class II

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Prepared by the NHS Commissioning Board Clinical Reference Group for

Pulmonary Hypertension

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Policy Statement

The NHS Commissioning Board (NHS CB) will commission treatments for patients with functional class II pulmonary hypertension in accordance with the criteria outlined in this document.

In creating this policy the NHS CB 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

The NHS CB 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.The NHS CB is committed to ensuring equality of access and non-discrimination, irrespective of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex (gender) or sexual orientation. In carrying out its functions, the NHS CB 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 they are responsible, including policy development, review and implementation.

Plain Language Summary

Pulmonary hypertension is a serious and progressive disease characterised by increasing limitations on physical activity, right heart failure and premature death. ‘Functional Class’ (FC) is a subjective classification for patients with pulmonary hypertension based on the patient’s answer to questions about limitations on their physical activity.

There is already a national policy for commissioning medicines to treat pulmonary hypertension that restricts funding to patients in functional classes III and IV. This policy is an addition to that policy, supporting the provision of medicines for highly selected patients at functional class II.

Specialist clinicians have identified criteria that can be used to identify a small number of patients (around 20 per year) in functional class II who are most likely to deteriorate and, therefore, benefit from early treatment with these medicines.

Patients in functional class II with poor prognostic features who meet the criteria outlined in this document will be eligible for treatment. The outcome for these patients will be used to inform future treatments.

1. Introduction

Pulmonary hypertension is a serious and progressive disease characterised by increasing limitations on physical activity, right heart failure and premature death.

Severity is often assessed based on WHO functional class (FC), ranging from I (no limitation in physical activity) to IV (symptoms at rest and limited physical activity).

The national policy for targeted therapies for the treatment of pulmonary hypertension in adults excludes patients in functional classes I and II. However, European consensus guidelines[1] recommend the use of targeted therapies in patients in functional class II. In addition, approval by the Scottish Medicines Consortium for the use of sildenafil and ambrisentan in Scotland implicitly supports the use of these medicines in treating patients in functional class II.[2,3]

Clinicians in England believe that patients meeting certain criteria in functional class II are likely to rapidly progress to functional class III and should be treated.

2. Definitions

Brain (or B-type) natriuretic peptide (BNP)

Both BNP and its N-terminal fragment (called **NT proBNP**) are polypeptides secreted by the ventricles of the heart in response to excessive stretching of heart muscle cells. BNP and NT prohormone BNP are used as indicators in the diagnosis of heart failure. Both markers are typically higher in patients with a worse outcome.

Cardiac index

Haemodynamic parameter that relates cardiac output to body surface area and provides an indicator of heart pump performance relative to the size of the person.

Cardiopulmonary exercise testing (CPET)

Non invasive testing of heart and lung function.

Endothelin receptor antagonists (ERA)

Class of medicines used in the treatment of PH that block the effects of endothelin, a peptide made by the body in the endothelium (a layer of cells which line the heart and blood vessels). Endothelin constricts blood vessels and elevates blood pressure. Includes selective A receptor blockers such as ambrisentan, and dual blockers, such as bosentan, than block both A and B endothelin receptors.

Functional class (FC)

Subjective classification for patients with pulmonary hypertension based on the patient's answer to questions about limitations on their physical activity. Ranges from FCI (no limitation of physical activity) to FCIV (symptoms on any physical activity and some symptoms at rest).

Pericardial effusion

Abnormal accumulation of fluid around the heart that can adversely affect heart function.

Phosphodiesterase type 5 inhibitors (PDE5i)

Class of medicines used in the treatment of PH that block the phosphodiesterase type 5 [PDE5] enzyme. Inhibiting this enzyme relaxes blood vessel walls, such as in the pulmonary arteries, increasing blood flow and reducing blood pressure. Sildenafil and tadalafil are licensed for the treatment of PH.

Pulmonary hypertension (PH)

Pulmonary hypertension (PH) is a rare disorder of the blood vessels in the lung defined as an increase in mean pulmonary artery pressure (PAP) of 25mmHg or greater at rest as assessed by right heart catheterisation. It 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.

Right arterial pressure (RAP)

The pressure of blood in the thoracic vena cava, near the right atrium of the heart; reflects the amount of blood returning to the heart and the ability of the heart to pump the blood into the arterial system.

Tricuspid Annular Plane Systolic Excursion (TAPSE)

Echocardiographic measure of right ventricle ejection fraction that is an independent prognostic value in patients with heart failure.

3. Aim and Objectives

To consider the inclusion in the national policy of certain patients with pulmonary hypertension in functional class II who meet clinical criteria associated with more rapid deterioration to functional class III.

The aim of this amendment is to

- Respond to clinical concerns about the lack of commissioned treatment options for patients in functional class II at risk of rapidly deteriorating to functional class III
- Improve consistency in commissioned clinical practice in England with that delivered in other European countries
- Delay disease progression in patients in functional class II with poor prognostic indicators
- Limit the economic impact of treating the identified patients through the use of the lowest cost targeted therapies (PDE5i) only.

4. Criteria for commissioning

Only a PDE5 inhibitors (PDE5i) will be commissioned for the treatment of patients with PH in functional class II who meet the following criteria:

- Elevated BNP or NT pro-BNP based on age and local range
- RAP> 8mm Hg and cardiac index < 2.5
- Pericardial effusion
- TAPSE <2cm
- CPET PVO2 <15 ml/min/Kg

The use, addition of, or switching to, any other class of targeted therapy is not commissioned.

In accordance with the national policy, the following PDE5 inhibitors will be commissioned:

Sildenafil (oral)

i) As Viagra tablets (unlicensed indication): for dose escalation 25-100mg three times daily

ii) As Revatio tablets: for use only at licensed dose of 20mg three times daily

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

5. Patient pathway

See national policy and service specification for pulmonary hypertension (designated services).

6. Governance arrangements

See national policy and service specification for pulmonary hypertension (designated services)

7. Epidemiology and needs assessment

See national policy and service specification for pulmonary hypertension (designated services).

An estimated 20 patients each year are believed to meet the above criteria for patients in functional class II with poor prognostic features. Such patients are currently treated in accordance with the national policy once they deteriorate to functional class III.

8. Evidence Base

1. North of England SCG (Yorkshire and the Humber office) commissioned the NIHR Centre for Reviews and Dissemination at the University of York to review the evidence for the use of targeted therapies in patients with pulmonary hypertension in functional class II (attached Level 1 evidence).[4]

This review concluded that "*Overall, few patients with functional class II disease have been included in randomised trials. Based on the published results of trials included in the most up-to-date systematic review, there is no clear evidence of benefit for any of the three dugs recommended by the ESC guidelines when compared to placebo in patients with functional class II disease*."

2. Only one randomised controlled trial, considered in the above review, has specifically assessed the effect of a targeted therapy on patients with PH functional class II. The EARLY study[5] compared bosentan with placebo for six months. Briefly, 93 patients were randomly assigned to bosentan and 92 to placebo.

The primary outcomes were pulmonary vascular resistance and six-minute walk distance (6MWD). At six months, geometric mean pulmonary vascular resistance was improved with bosentan [83.2% (95% confidence interval 73.8 to 93.7) of the baseline value in the bosentan group and 107.5% (97.6 to 118.4) of baseline value in the placebo group; net treatment effect of bosentan was -22.6% (-33.5 to -10.0, p<0.0001)]. However, there was no significant improvement in 6MWD [+11.2 m (-4.6 to 27.0) in the bosentan group vs -7.9 m (-24.3 to 8.5) in the placebo group; mean difference 19.1 m, 95% CI –3.6 to 41.8m, p=0.0758 NS]. Baseline 6MWD values were 438 m in the bosentan group and 431 m in the placebo group so the net treatment effect of 19.1 m (3.6 to 41.8) seems unlikely to be clinically significant.

Bosentan delayed time to clinical worsening (secondary outcome measure) (hazard ratio 0.227, 95% CI 0・065–0・798; p=0.0114) with fewer patients in the bosentan group reaching at least one of the components of clinical worsening by month 6 than did those in the placebo group. Bosentan treatment was associated with a lower incidence of worsening functional class (secondary outcome measure) compared with placebo (3 [3.4%] patients in the bosentan group vs 12 [13.2%] in the placebo group, p=0.0285).

3. Other randomised placebo-controlled studies of targeted therapies (including ambrisentan and sildenafil) in mixed populations of patients with functional class II-IV have demonstrated similar delays in clinical worsening compared with placebo.[6-9] However, as concluded in the Centre for Reviews and Dissemination (CRD) report, it is difficult to determine a specific effect on disease progression in

patients in functional class II.

4. Unpublished data from one long-term follow up study (ARIES-E)[10] indicates that patients in functional class II previously randomised to placebo in clinical trials do not catch-up with those on active treatment (ambrisentan) when switched to active therapy. In the ARIES-E study, a total of 383 patients, previously enrolled in one of two identical randomised placebo-controlled trials (ARIES-1 and ARIES-2[6]), received ambrisentan for 2 years. Figure 1 follows the 6MWD on ambrisentan for a total of 153 patients in functional class II who had previously been treated with placebo or ambrisentan. While those previously treated with placebo gain a mean of around 20m in 6MWD from baseline, this is less than in those previously treated with ambrisentan. These data suggest that delaying treatment disadvantages patients in functional class II.

9. Rationale behind the policy statement

There is weak evidence, based on secondary outcome measures in randomised controlled trials and post-hoc sub-group analysis that targeted therapies delay time to clinical worsening for patients in functional class II, and that patients who do not receive treatment do not catch-up with those who receive active treatment earlier.

Specialist clinicians have identified prognostic criteria that can be used to identify a small cohort (around 20 patients pa) of patients in functional class II who are most likely to deteriorate and, therefore, benefit from early treatment with a targeted therapy.

Since evidence to support this proposal is not robust, clinicians propose use of only the lowest cost targeted therapies (sildenafil, tadalafil). At a basic price of around £6,000 pa, the cost impact of implementing this amendment for around 20 patients would be around £125,000 pa.

10. Mechanism for funding

Through the responsible Area Team.

11. Audit Requirements

National PH database will be used to monitor implementation of this amendment.

12. Documents which have informed this policy

See References

13. Links to other policies

National policy for targeted therapies for the treatment of pulmonary hypertension in adults

14. Date of Review

This policy will be reviewed in April 2014 unless data received indicates that the proposed review date should be brought forward or delayed.

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