Interim Commissioning Policy

Target therapies for the treatment of pulmonary arterial hypertension in Adults

POLICY PUBLISHED: 1 JULY 2008
POLICY REVISED: 14 JANUARY 2009
REVIEW DATE: 1 JULY 2009
1 BACKGROUND

In April 2008 the commissioning of pulmonary arterial hypertension (PAH) became the direct responsibility of the 10 Specialised Commissioning Groups (SCGs) in England. These are supra-regional services. As a consequence it was considered beneficial to have a single national commissioning policy operating across England.

2 CAVEATS

This is an interim policy pending the publication of the NICE Technology Appraisal Guidance due in April 2008. When the NICE Guidance is published the policy will be reviewed.

The policy has drawn on available clinical effectiveness evidence. It has also taken into account affordability and other priorities of Primary Care Trusts.

The Consensus Statement, produced by the consultant staff who specialise in the care and treatment of patients with pulmonary arterial hypertension has been taken into consideration in drawing up this policy.¹

It is anticipated that the national pulmonary arterial hypertension commissioning group working under the auspices of the National Specialised Commissioning Group will review this commissioning policy on an annual basis.

3 SCOPE OF POLICY

The policy focuses on the use of the high cost disease targeted therapies in the treatment of pulmonary hypertension in adults.

This commissioning policy needs to be read in conjunction with the national service specification for the pulmonary hypertension service.

4 PULMONARY HYPERTENSION

4.1 Definition

Pulmonary arterial hypertension (PAH) is a rare disorder of the blood vessels in the lung in which the pressure in the pulmonary artery rises above normal levels and may become life threatening.

It is caused by a diverse group of diseases and is characterised by a progressive increase of pulmonary vascular resistance leading to right ventricular failure and premature death if untreated.

¹ Consensus Statement of the management of pulmonary hypertension in clinical practice in the UK and Ireland; Heart, March 2008, volume 94 Supplement 1
PAH is defined as a mean pulmonary artery pressure greater than 25mm Hg at rest or greater than 30 mm Hg on exercise.

4.2 Signs and Symptoms

Pulmonary hypertension is associated with disparate conditions including connective tissue disease, congenital heart diseases, chronic pulmonary thromboembolism, sickle cell disease, HIV infection, use of an appetite suppressant, and liver disease. If the cause is unknown then it is referred to as idiopathic pulmonary arterial hypertension (IPAH). IPAH can occur sporadically or can be familial.

The cardinal symptom, breathlessness, is shared with many more common diseases and the signs of pulmonary hypertension are difficult to elicit. The delay between onset of symptoms and diagnosis is often as long as two years.

In the past, treatments for pulmonary hypertension were limited, but now there is a range of drug therapies in use that have been shown to improve the outcome of PAH.

4.3 Incidence and Prevalence

Lack of systematic and often poor data collection prevents reliable estimation of incidence, morbidity, mortality and survival.

The potential “pool” of patients to be treated is complex and based on a number of factors as shown below:

- Incidence
- Diagnosis Rate
- Referral Rate
- Take on Rate
- Prevalence

- Pool of PAH patients on drug treatment

- Death Rate
- Transplantation Rate
- Endarterectomy Rate
- Withdrawal of Treatment

Changes to natural history of the disease as a result of treatment i.e. increased survival

The census of patients on treatment at 31 March 2007 identified 1500 patients UK wide. The number has doubled over 3 years.

The pool of patients on treatment continues to grow and has not yet reached a ‘steady state’.

4.4 Diagnosis

IPAH is a diagnosis of exclusion. Admission is usually necessary in order to carry out a series of investigations regarding cause, baseline pulmonary haemodynamics and responsiveness to potential therapy.
The diagnostic evaluation of PAH includes the following: 12-lead electrocardiogram, chest radiograph, echocardiogram, cardiopulmonary exercise testing (6 minutes walk or shuttle test), ventilation perfusion lung scan, high resolution CT scan, CT pulmonary angiogram and pulmonary function tests and in selected cases MRI and pulmonary angiography. Liver function and thyroid function studies, collagen vascular screen, and HIV antibody are useful in determining whether PAH is associated with systemic disorders.

Diagnosis is made at the time of right heart catheterisation (although in very sick unstable patients this may be dangerous and treatment may be commenced in the absence of catheter data if other indicators are consistent with severe disease). It is performed primarily to confirm the diagnosis of PAH and as indicator of disease severity. Cardiopulmonary haemodynamic measurement and vasoreactivity testing is performed to help guide therapy in selected patients, and decide on the appropriateness of calcium antagonist therapy.

5 TREATMENT CENTRES

Six centres have been designated by the National Commissioning Group (NCG) 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.

A service specification including standards for the delivery of care has been agreed and each centre is measured against these standards by the National Commissioning Group (NCG).

The designated centres are:

- **London**
  - Hammersmith Hospital
  - Royal Brompton Hospital
  - Royal Free Hospital
- **Cambridge**
  - Papworth Hospital
- **Sheffield**
  - Royal Hallamshire Hospital
- **Newcastle**
  - Freeman Hospital

NB: Great Ormond Street Hospital is designated to provide pulmonary hypertension services for children. This service is funded centrally by National Commissioning Group.

Each centre has an agreed action plan to enable them to move towards meeting all the standards.

There are discussions in progress to support the development of shared care arrangements with appropriate local clinical services. There are also discussions taking place about links with the designated services for grown up congenital heart disease.
6.1 List of drugs covered and approved doses

<table>
<thead>
<tr>
<th>Oral</th>
<th>Nebulised</th>
<th>Subcutaneous</th>
<th>Intravenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bosentan 125mg bd only</td>
<td>• Iloprost</td>
<td>• Treprostinil*</td>
<td>• Epoprostenol*</td>
</tr>
<tr>
<td>• Sildenafil (Revatio – 20mg tds only</td>
<td></td>
<td></td>
<td>• Iloprost*</td>
</tr>
<tr>
<td>(Viagra 25mg-100mg tds only)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sitaxsentan 100mg od only</td>
<td></td>
<td>• Treprostinil*</td>
<td></td>
</tr>
</tbody>
</table>

* Prostaglandins

The approximate drug costs are shown below. Some dosages of some drugs will be variable.

<table>
<thead>
<tr>
<th></th>
<th>Cost without homecare</th>
<th>Cost with homecare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosentan 125mg BD</td>
<td>£23,500</td>
<td>£21,000</td>
</tr>
<tr>
<td>Sitaxsentan 100mg</td>
<td>£23,500</td>
<td>£21,000</td>
</tr>
<tr>
<td>IV Iloprost</td>
<td>£39,000</td>
<td>£37,000</td>
</tr>
<tr>
<td>Nebulised Iloprost (Ventafee)</td>
<td>£32,200</td>
<td>£31,500</td>
</tr>
<tr>
<td>Treprostinil</td>
<td>£41,500</td>
<td>£35,200</td>
</tr>
<tr>
<td>Epoprostenol (incl pump)</td>
<td>c £35,000</td>
<td>£33,000</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>£5,440 - £6,700</td>
<td>£5,000 - £6,700</td>
</tr>
</tbody>
</table>

Doses above those specified will not normally be funded.

6.2 Monotherapy

6.2.1 Monotherapy will be provided for patients as described in table 1.

Other conditions are currently excluded. Any extension to the range of conditions will only be considered as a service development. These will be subject to business case assessment as set out in Schedule 6 of the NHS Contract.

6.2.2 Patients only with a functional classification of PAH of stage III or stage IV of the WHO modified New York Heart Association (NYHA) Classification will be funded. Patients with functional Class I or II on baseline assessment will not normally be eligible for funding save in exceptional circumstances (as defined in Section 6.4)

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.

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

6.2.3 Drug doses higher than those specified in section 6.1 will not normally be eligible for funding save in exceptional circumstances (as defined in section 6.4).

6.3 **Dual Therapy**

6.3.1 Dual therapy will only be funded in combinations involving sildenafil unless there are exceptional circumstances.

6.4 **Exceptionality**

Responsibility for demonstrating exceptionality rests with the requesting clinician.

Only evidence of clinical need will be taken into consideration. Factors such as gender, ethnicity, age, lifestyle or other social factors such as employment or parenthood will not be considered on grounds of equality.

In order to demonstrate exceptionality the patient:

- Must be *significantly different* to the population of interest (ie patients with pulmonary hypertension and/or the subpopulation).

AND

- Be more likely to benefit from this intervention than might be expected than other patients with the condition.

The fact that the treatment might be efficacious for the patient is not, in itself, grounds for exceptionality.

If a patient’s clinical condition matches certain indications which might be seen as “accepted” (e.g. the trial indication, the licensed indication,
anecdotal or routine but unstudied clinical practice) etc) but these particular indications fall outside the commissioning policy, the patient is, by definition, not exceptional.

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

6.4.1 Dual therapy: for patient switching from one mono-therapy to an alternative mono-therapy (up to a maximum of 12 weeks)

6.4.2 Dual therapy: for patients who have been listed for the following surgery may be given additional consideration:

- Heart-lung transplantation
- Double Lung transplantation
- Thrombo-endarterectomy (in patients with chronic thrombo-embolic disease)

6.4.3 Continuation of existing treatments (including a prostacyclin) 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.

6.4.4 Continuation of existing treatments (including a prostacyclin) 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.

In those situations where the principle of exceptionality cannot be applied (i.e. in situations where there is no reference group such as funding requests for very rare clinical conditions or complications) then the following will be considered: the nature of the condition, the nature of the treatment, consideration of the biological plausibility that this treatment might work in this clinical situation, an assessment of value for money and prioritisation against other competing demands.

6.5 Clinical Trials

The commissioners will not pick up the funding of patients coming off drug company sponsored drug trials / extended access programmes or compassionate funding unless prior arrangements have been made.

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

The commissioners will fund patients once the service development has been agreed.
6.6 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:-

a) Successful surgery
b) Clinically relevant side-effects eg liver function
c) Poor/no response to treatment

Drug therapies may also be withdrawn “at the end of life”.
<table>
<thead>
<tr>
<th>Pulmonary Arterial Hypertension (IPAH, FPAH, Anorexogen-induced, and where associated with Portal hypertension or HIV infection)</th>
<th>PAH associated with significant venous or capillary involvement</th>
<th>PAH associated with connective tissue disease</th>
<th>PAH associated with congenital heart disease</th>
<th>PH due to chronic thrombotic and/or embolic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line</strong></td>
<td>WHO II: S WHO IV: P</td>
<td>PVOD only: WHO III/IV, S, consider surgery PCH: no disease targeted treatment supported consider surgery</td>
<td>WHO III/IV: B</td>
<td>WHO III/IV: S Consider surgery</td>
</tr>
<tr>
<td><strong>Second line/ Alternative</strong></td>
<td>WHO III: B, P or X WHO IV: B</td>
<td>WHO III/IV: S, P or X</td>
<td>WHO III/IV: B</td>
<td></td>
</tr>
<tr>
<td><strong>Combination</strong></td>
<td>B+S or X+S Patients should be entered into a clinical trial where possible</td>
<td>B+S or X+S Patients should be entered into a clinical trial where possible</td>
<td>B+S will be considered as a bridge to surgery</td>
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</tr>
<tr>
<td><strong>Alternate combination</strong></td>
<td>P+S Patients must be entered into a clinical trial (NB trial participation previously agreed by commissioners)</td>
<td>No published data on use of B or X Case reports only on S and only in PVOD</td>
<td>No RCT evidence but some evidence of functional improvement on B, X and S Long term follow-up data is poor Evidence on P is equivocal No published evidence of benefit of combination.</td>
<td>RCT evidence of functional improvement in WHO III with B (BREATHE-5) No published evidence of benefit of combination. Case reports on distal (inoperable) disease treated by B (BENEFIT). No published data on use of X.</td>
</tr>
</tbody>
</table>

**Evidence**

- Few head to head studies, clinical consensus only.
- RCT evidence of comparable results between S and B (SERAPH)
- RCT and extension evidence of survival benefit of S (SUPER 1)
- RCT evidence of functional improvement over placebo for B (BREATHE 1) and X (STRIDE 1)
- RCT and extension evidence of survival benefit of P but no firm evidence of relative efficacy of different preparations in class
- Some small study evidence of improved results in combination of S+B

**B**= Bosentan, **P**= Prostanoids, **S**= Sildenafil, **X**= Sitaxsentan OR Ambrisentan

**WHO**= Functional classification of PH modified after the New York Heart Association functional classification according to the World Health Organisation 1998

**IPAH**= Idiopathic PAH; **FPAH**= Familial PAH; **PVOD**= Pulmonary veno-occlusive disease; **PCH**= Pulmonary capillary haemangiomatosis

* If first line is contraindicated, ineffective in controlling symptoms or poorly tolerated
7 FUNDING APPROVAL

There will be no requirements to seek commissioner approval prior to the commencement of treatment

BUT

the release of commissioner funding is dependent on registration of the patient on the national database AND provision of the commissioner dataset.

The commissioner dataset is as follows: -

- Patients NHS number
- Patients DoB and postcode
- GP Practice Code
- Name of drug

Expected maintenance dose: -

- Cost of drug
- Starting date for treatment
- Projected cost to year end
- Primary diagnosis (i.e. underlying condition)
- WHO/NYHA Functional Classification

8 MONITORING INFORMATION

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

9 REVIEW

This policy will be reviewed on an annual basis and/or in the light of any new clinical or cost effectiveness evidence.

New treatment regimens will not be considered in year unless there is evidence of a sustainable benefit.
New drugs coming onto the market may be added to the list in year via the commissioners under the following circumstances:

- If they have the same or greater efficacy than current drugs

AND

- If they have an equivalent or lower cost to current treatment

10 FURTHER WORK TO BE UNDERTAKEN

Further work will be undertaken to review/collect cost effectiveness evidence. Once this information is available the policy will be reviewed.

14 January 2009 (V2 Final document)

Appendix A

POLICY CHANGE PROTOCOL

The key steps in the policy change protocol are as follows:

(a) All requests for changes to the national policy should be made to the lead SCG Director in writing.

(b) The change request should clearly set out the evidence supporting the change, the anticipated benefits, and any financial implications.

(c) Requests from the clinicians should come via the national clinicians group with the chair of the group writing formally to the lead SCG Directors.

(d) The lead SCG Director will obtain a public health/specialist pharmacist review of the clinical and cost effectiveness and the cost implications.

(e) The original request and the public health/specialist pharmacy opinion will be considered by the national PH Commissioners Forum.

(f) The national PH Commissioners Forum will make a recommendation to SCGDN.