

**NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE**

**Proposed Health Technology Appraisal**

**Drugs for the treatment of pulmonary arterial hypertension**

**Draft scope**

**Draft remit / appraisal objective:**

To appraise the clinical and cost effectiveness of treatments for pulmonary hypertension within their licensed indications.

**Background:**

Pulmonary hypertension is defined as a mean pulmonary artery pressure greater than 25 mmHg at rest, or greater than 30 mmHg on exercise. People with primary pulmonary hypertension (PPH) have no underlying disease causing the elevation in pulmonary artery pressure. Primary pulmonary hypertension is a form of pulmonary artery hypertension (PAH). Other forms of PAH are associated with conditions such as connective tissue diseases, congenital heart disease, portal hypertension, drugs (e.g. dexfenfluramine) and HIV. These other forms of PAH were previously known as secondary pulmonary hypertension, but this term has now been abandoned because it is without value for diagnosis and decisions on treatment.

PAH is characterised by pulmonary arterial vasoconstriction, vascular remodelling (proliferation of vascular smooth muscle with intimal thickening and fibrosis which narrows the blood vessel). Symptoms of PAH include breathlessness especially with physical activity, fatigue, chest pain, palpitations, fainting, and oedema which worsen as the disease progresses. PAH if untreated leads to a progressive increase in pulmonary vascular resistance, right ventricular failure and death.

The estimated incidence of PAH (PPH and other types of PAH combined) is two to four cases per million per year which approximates 100-200 new cases of PAH in England and Wales per year. Prevalence figures are difficult to estimate.

The aims of treatment are to prevent progression of the disease, prevent pulmonary artery thrombosis, and to decrease the pulmonary arterial pressure, preferably in conjunction with an increase in cardiac pressure. They include specific treatment where the cause is known (e.g. pulmonary thromboendarterectomy for thromboembolic PAH) and / or treatments to relieve the symptoms of PAH. Symptomatic treatments of PAH include pharmaceutical treatment with vasodilators in the form of calcium channel blockers (CCBs) in combination with anticoagulants, digoxin and diuretics. Some people may also require supplemental oxygen if their oxygen saturation is low at night or if breathing becomes difficult. Individuals with chronic PAH which is

unresponsive to medical management may be referred for a lung or heart-lung transplant.

### **The technologies:**

Epoprostenol (also known as prostacyclin) is a naturally occurring prostaglandin (prostaglandin I<sub>2</sub>) that causes vasodilatation and prevents platelet aggregation. It has a very short half life. Iloprost, treprostinil and beraprost are stable analogues of epoprostenol.

Epoprostenol injection (Flolan, GlaxoSmithKline) is licensed for the treatment of primary pulmonary hypertension (PPH) in NYHA functional class III and IV patients who do not respond adequately to conventional therapy. It is administered by continuous intravenous infusion.

Iloprost nebuliser solution (Ventavis, Schering Plough) is licensed for the treatment of patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms. It is administered using a compressed air nebuliser between six and nine times daily.

Treprostinil (Remodulin, United Therapeutics) and beraprost (Berasil, Aventis Pharma) do not currently have UK marketing authorisations. Treprostinil injection is licensed in the USA. It is administered as a continuous subcutaneous infusion. Beraprost is the first orally active prostacyclin analogue. It is approved for the treatment of pulmonary hypertension in Japan.

Bosentan (Tracleer, Actelion Pharmaceuticals) is an endothelin receptor antagonist, which is licensed for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with grade III functional status.

Sildenafil citrate (Viagra, Pfizer) is a phosphodiesterase 5 inhibitor with the ability to potentiate selective pulmonary vasodilation (smooth muscle relaxation in the lung) without systemic hypotension. However, it is currently not licensed for the treatment of PAH in the UK.

<b>Intervention(s)</b>	Therapies that include at least one of the following: <ul style="list-style-type: none"> <li>• epoprostenol (by continuous intravenous infusion)</li> <li>• iloprost (inhaled)</li> <li>• treprostinil (by continuous subcutaneous infusion)</li> <li>• beraprost (oral)</li> <li>• bosentan (oral)</li> <li>• sildenafil (oral)</li> </ul>
<b>Population(s)</b>	Adults and children with a diagnosis of pulmonary arterial hypertension.
<b>Current standard comparators</b>	Strategies without any of the above listed interventions
<b>Outcomes</b>	The outcome measures to be considered include: <ul style="list-style-type: none"> <li>• survival</li> <li>• exercise capacity</li> <li>• symptomatic improvements</li> <li>• frequency of hospitalisation and GP visits</li> <li>• lung or heart-lung transplantation</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life</li> <li>• haemodynamic assessment (e.g. cardiac index, right atrial pressure, pulmonary arterial oxygen saturation, pulmonary arterial pressure and pulmonary vascular resistance)</li> </ul>
<b>Economic analysis</b>	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.  The time horizon for the economic evaluation should reflect the period over which costs and benefits can reasonably be expected given the prognosis of PAH  Costs will be considered from an NHS and Personal Social Services perspective.

<p><b>Other considerations</b></p>	<p>The interventions will be appraised according to their anticipated licensed indications. Guidance will only be issued in accordance with relevant marketing authorisations.</p> <p>Where the evidence allows, subgroups of patients with PAH who are more likely to benefit from these drugs should be identified.</p> <p>Regimens containing any of the drugs listed under interventions, either alone or in combination, may be compared to each other.</p>
<p><b>Related NICE recommendations</b></p>	<p>Related Technology Appraisals:       None</p> <p>Related Guidelines:                       None</p>

**Questions for consultation**

The Institute seeks views on whether / which of the interventions should be considered adjuncts to other treatments.

The Institute seeks views on the appropriateness of comparing the clinical and cost-effectiveness of these interventions with each other.

The Institute seeks views on the appropriateness of excluding newborns from this appraisal.