Remit / Appraisal objective:
To appraise the clinical and cost effectiveness of treatments for pulmonary arterial hypertension (PAH) within their licensed indications.

Background
Pulmonary arterial hypertension (PAH), is a group of diseases characterised by a progressive increase of pulmonary vascular resistance leading to right ventricular failure and premature death. It is defined by a mean pulmonary artery pressure greater than 25 mmHg at rest, or greater than 30 mmHg on exercise.

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. PAH is associated with significant mortality: before the availability of disease-specific therapy, the median survival of people with idiopathic PAH (see below) was 2.8 years. Mortality in those with PAH related to connective tissue disease is even higher.

The revised clinical classification of pulmonary hypertension (2003) groups different types of pulmonary hypertension, including PAH, according to the cause or mechanism of the disease, clinical presentation and therapeutic options. There are five groups within this classification. PAH is categorised as group 1, and group 1 is further subcategorised as follows:

1.1 idiopathic PAH
1.2 familial PAH
1.3 PAH associated with other conditions, including PAH associated with the following: connective tissue disease (1.3.1), congenital systemic to pulmonary shunts (1.3.2), portal hypertension (1.3.3), HIV infection (1.3.4), drugs and other toxins (1.3.5), and various other conditions (1.3.6),
1.4 PAH associated with significant venous or capillary involvement including pulmonary veno-occlusive disease (1.4.1) and pulmonary artery haemangiomatosis (1.4.2)
1.5 Persistent pulmonary hypertension of the newborn.
Appendix A

Groups 2-4 of the classification are as follows: pulmonary hypertension associated with left heart diseases (group 2), pulmonary hypertension associated with lung respiratory diseases and/or hypoxia (group 3), pulmonary hypertension due to chronic thrombotic and/or embolic disease (Group 4), and miscellaneous conditions (group 5). These groups are also further subdivided.

In addition to the clinical classification, PAH can also be classified according to functional capacity. The NYHA/WHO classification of functional status of patients with pulmonary hypertension stratifies patients into four groups as follows:

I no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnoea, fatigue, chest pain or pre-syncope.

II mild limitation of physical activity: there is no discomfort at rest, but normal physical activity causes increased dyspnoea, fatigue, chest pain or pre-syncope.

III marked limitation of physical activity: there is no discomfort at rest, but less than ordinary activity causes increased dyspnoea, fatigue, chest pain or pre-syncope.

IV unable to perform any physical activity and may have signs of right ventricular failure at rest: dyspnoea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

The estimated incidence of PAH is two to four cases per million per year which approximates 100-200 new cases of PAH in England and Wales per year. Prevalence of severe PAH is estimated at between 30 and 50 cases per million population.

The aims of treatment are to prevent progression of the disease, prevent pulmonary artery thrombosis, relieve the symptoms of PAH, improve exercise capacity and prolong survival. Pharmacological treatments of PAH include anticoagulants, digoxin and diuretics. Some patients with idiopathic PAH respond to calcium channel blockers. Supplemental oxygen may be required in people with oxygen saturation is low at night or if breathing becomes difficult. Individuals with PAH which is unresponsive to medical management may be referred for a lung or heart-lung transplant.

The technologies

Prostacyclin is a naturally occurring prostaglandin (prostaglandin I2) that causes vasodilatation, prevents platelet aggregation and inhibits vascular proliferation. It has a very short half life. Epoprostenol is a synthetic prostacyclin. Iloprost, treprostinil and beraprost are stable analogues of epoprostenol.

Epoprostenol injection (Flolan, GlaxoSmithKline) is licensed for the treatment of primary pulmonary hypertension (under the 2003 classification this would
correspond to idiopathic and familial PAH) NYHA functional class III and IV in patients who do not respond adequately to conventional therapy. It is administered by continuous intravenous infusion.

Iloprost nebuliser solution (Ventavis, Schering Healthcare) 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. Iloprost by continuous intravenous infusion is also used in the treatment of pulmonary hypertension, but the intravenous product does not have a UK marketing authorisation.¹

Bosentan (Tracleer, Actelion Pharmaceuticals) is a non-selective 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. The summary of product characteristics states that efficacy has been shown in primary PAH and PAH secondary to scleroderma without significant interstitial pulmonary disease. This would correspond to subgroups 1.1, 1.2, 1.3.1 under the 2003 classification (see above).

Sitaxentan (Thelin, Encysive [UK]) is a selective endothelin A receptor antagonist, which holds a UK marketing authorisation for the treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity. The summary of product characteristics states that efficacy has been shown in primary pulmonary hypertension and in pulmonary hypertension associated with connective tissue disease (this would correspond to subgroups 1.1, 1.2, 1.3.1 see above).

Sildenafil citrate (Revatio, Pfizer) is a phosphodiesterase 5/6 inhibitor with the ability to potentiate selective reduction in pulmonary vascular tone (pulmonary vasodilation) when given orally with little systemic hypotension. It holds a UK marketing authorisation for the treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity. The summary of product characteristics states that efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease (this would correspond to subgroups 1.1, 1.2, 1.3.1 see above).

¹ Intravenous iloprost will not be included in this appraisal. Products without UK marketing authorisation for the indication concerned are not included in NICE Technology Appraisals.
### Appendix A

| Intervention(s) | Therapies that include at least one of the following:  
|                | • epoprostenol (by continuous intravenous infusion)  
|                | • iloprost (inhaled)  
|                | • bosentan (oral)  
|                | • sitaxentan (oral)  
|                | • sildenafil (oral)  
|                | The use of combination regimens involving more than one of the above technologies will be considered if the evidence allows. |
| Population(s)  | Adults with pulmonary arterial hypertension (Category 1 of the revised Venice classification of pulmonary hypertension 2003) in NYHA/WHO functional classes III and IV for whom calcium channel blockers are inappropriate or no longer effective. |
| Current standard comparators | • Supportive treatments including digoxin, diuretics, anticoagulants, oxygen  
| | • The treatments listed under intervention above will be compared with each other.  
| | • If the evidence allows, intravenous iloprost may be considered as a comparator |
| Outcomes | The outcome measures to be considered include:  
| | • survival  
| | • health-related quality of life  
| | • exercise capacity  
| | • symptomatic improvements  
| | • frequency of and duration of hospitalisation and outpatient / GP visits  
| | • time to clinical deterioration (e.g. alternative therapy including switch of drug therapy, or lung transplantation)  
| | • adverse effects of treatment  
| | • haemodynamic assessment (e.g. cardiac index, right atrial pressure, pulmonary arterial oxygen saturation, pulmonary arterial pressure and pulmonary vascular resistance) |
### Economic analysis

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.

### Other considerations

The interventions will be appraised according to their anticipated licensed indications. Guidance will only be issued in accordance with relevant marketing authorisations.

**Any intervention that does not receive UK marketing authorisation within the required timelines will be excluded from the appraisal.**

Where the evidence allows, subgroups of patients with PAH who are more likely to benefit from these drugs should be identified, for example subgroups according to the 2003 clinical classification.

Regimens containing any of the drugs listed under interventions, either alone or in combination, may be compared to each other.

### Related NICE recommendations

Related Technology Appraisals: None

Related Guidelines: None