

**REGIONAL DRUG AND THERAPEUTICS CENTRE
(NEWCASTLE)**

**CURRENT THERAPEUTIC STRATEGIES FOR
PULMONARY ARTERIAL HYPERTENSION**

**Wolfson Unit
Claremont Place
Newcastle upon Tyne
NE2 4HH**

March 2009



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CONTENTS

SUMMARY	6
BACKGROUND.....	8
EFFICACY.....	10
PROSTACYCLINS	10
<i>Epoprostenol</i>	10
<i>Iloprost</i>	11
ENDOTHELIN ANTAGONISTS	12
<i>Bosentan</i>	12
<i>Sitaxentan</i>	14
<i>Ambrisentan</i>	16
PHOSPHODIESTERASE INHIBITORS.....	17
<i>Sildenafil</i>	17
ADVERSE EFFECTS	19
PROSTACYCLINS	19
<i>Epoprostenol</i>	19
<i>Iloprost</i>	20
ENDOTHELIN ANTAGONISTS	20
<i>Bosentan</i>	20
<i>Sitaxentan</i>	21
<i>Ambrisentan</i>	21
PHOSPHODIESTERASE INHIBITORS.....	21
<i>Sildenafil</i>	21
ARRANGEMENTS FOR PRESCRIBING.....	22
DOSAGE, ADMINISTRATION AND COST.....	22
PROSTACYCLINS	22
<i>Epoprostenol</i>	22
<i>Iloprost</i>	23
ENDOTHELIN ANTAGONISTS	23
<i>Bosentan</i>	23
<i>Sitaxentan</i>	24
<i>Ambrisentan</i>	24
PHOSPHODIESTERASE INHIBITORS.....	25
<i>Sildenafil</i>	25

PLACE IN TREATMENT	26
FUNCTIONAL CLASS II	28
<i>First choice</i>	28
<i>Second choice</i>	28
FUNCTIONAL CLASS III	28
<i>First choice</i>	28
<i>Second choice</i>	29
<i>Third choice</i>	29
FUNCTIONAL CLASS IV.....	30
COMBINATION THERAPY.....	30
SWITCHING THERAPIES.....	30
FUTURE DEVELOPMENTS	31
ACKNOWLEDGEMENTS	31
REFERENCES	32
APPENDICES	36
APPENDIX 1. Revised Clinical Classification of Pulmonary Hypertension (Venice 2003) ...	36
APPENDIX 2. NYHA/WHO Classification of Functional Status of Patients with PAH	37
APPENDIX 3. Summary of key trials	38

ABOUT THIS REPORT

This is one of a series of evaluations prepared by the Regional Drug and Therapeutics Centre (Newcastle). The aim is to give objective information and guidance to commissioners of health services, prescribers and others both on clinical aspects of the subject and on arrangements for prescribing. The reports are prepared by a multidisciplinary team within the Centre and reviewed by health authority personnel and appropriate external specialists. However, responsibility for the content and conclusions rest solely with the Regional Drug and Therapeutics Centre. We welcome comments on reports and suggestions for future topics. The following reports are available:

Subject	Date issued
The use of lapatinib in the management of metastatic breast cancer	November 2008
The use of liposomal doxorubicin in the management of metastatic breast cancer	October 2008
The use of dasatinib in the management of acute lymphoblastic leukaemia in adults	August 2008
The use of bevacizumab in the management of metastatic breast cancer	September 2007
The use of entecavir in the management of chronic hepatitis B infection	March 2007
The use of natalizumab in the management of multiple sclerosis	March 2007
The use of aromatase inhibitors in the treatment of early stage breast cancer (N)	March 2007
Palonosetron for the prevention of nausea and vomiting associated with cancer chemotherapy	March 2007
Alemtuzumab in the management of chronic lymphocytic leukaemia	March 2007
Omalizumab in the management of severe, persistent, allergic asthma	June 2006
Bortezomib second-line in the management of multiple myeloma	March 2006
Adjuvant docetaxel or paclitaxel in the management of early stage breast cancer (N)	March 2006
Erlotinib in the management of non-small cell lung cancer	March 2006
Ibritumomab in the management of B-cell follicular non-Hodgkin's lymphoma	March 2006
Rituximab in combination with CVP chemotherapy for the management of follicular non-hodgkins lymphoma.	March 2006
Pemetrexed in the management of malignant pleural mesothelioma	February 2006
Pegvisomant in the management of acromegaly	January 2006

Older reports are available via our website or on request

Agents which have been reviewed by the National Institute for Health and Clinical Excellence (NICE) are indicated by **(N)** after the report name. Please refer to the NICE website to access their guidance for these agents/conditions.

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SUMMARY

- Pulmonary arterial hypertension (PAH) is a severely disabling progressive disease of the pulmonary vascular system, which in the absence of aggressive treatment may lead to right-heart failure and premature death.
- PAH is defined as a mean pulmonary artery pressure (PAP) of ≥ 25 mmHg at rest and/or >30 mmHg on exertion, with a mean pulmonary capillary wedge pressure of ≤ 15 mmHg. It is classified according to clinical and pathological features and by functional capacity.
- Approximately two to eight patients per million develop the disease annually, which approximates to 100 - 350 new cases of PAH in England per year. The estimated prevalence is between 15 and 26 cases per million of the population.
- Clinically, patients with PAH most commonly present with dyspnoea and fatigue. Symptoms are generally progressive and may be accompanied by anginal chest pains and syncope, often upon exertion. The median life expectancy after diagnosis is 2.8 years without aggressive therapy.
- Treatment for PAH includes lifestyle modifications, conventional treatments and disease-specific treatments which should only be initiated in specialist centres by clinicians experienced in the management of PAH.
- Newly diagnosed patients should undergo acute vasoreactivity testing and those demonstrating a positive response should be considered as candidates for oral calcium channel blockers (CCBs). Patients with PAH who are not candidates for, or who have failed CCB therapy should be considered for long-term disease-specific therapy.
- Three classes of drugs (prostacyclins, endothelin receptor antagonists and phosphodiesterase-5 inhibitors), have shown efficacy in the treatment of adults with PAH in whom CCBs are inappropriate or no longer effective.
- Non-responders to vasoreactivity testing should be considered candidates for one of the four currently approved oral therapies (bosentan, sildenafil, sitaxentan, or ambrisentan).
- The clinical benefit in the short-term appears to be comparable for all oral therapies, with each demonstrating significant improvements in exercise capacity. The results with respect to clinical worsening or change in functional capacity are more variable, with significant improvements being observed in some studies, but not in others.
- Bosentan and ambrisentan are the only targeted therapies currently approved in the UK for the treatment of patients with PAH in functional class II.
- The quality and weight of evidence supports the use of bosentan as the first choice treatment in patients with PAH in functional class III. However, monthly liver function testing is required for all patients receiving an endothelin receptor antagonist.

- **Patients with liver abnormalities, or an inability to have liver function monitored on a monthly basis should be considered for treatment with sildenafil. It requires no specific laboratory monitoring, and has significant cost advantages over other agents used in the treatment of PAH. However, patients with ocular disease or recurrent epistaxis may be better candidates for other oral therapies.**
- **The newer agents ambrisentan and sitaxentan appear to have a benefit to risk ratio similar to that of bosentan in functional class III patients, but long-term data are lacking.**
- **Patients with more advanced disease in functional class III may require treatment with a prostacyclin. Both intravenous epoprostenol and inhaled iloprost have demonstrated significant improvements in exercise capacity and haemodynamics.**
- **Iloprost has a relatively short duration of action and requires six to nine daily inhalations to maintain the desired clinical effect and should be considered only as an alternative therapy for patients who fail or cease to tolerate oral therapy.**
- **Epoprostenol requires continuous infusion through a central venous catheter and has been associated with significant adverse events related to the delivery system. Because of the complexity of administration, epoprostenol should generally be reserved for patients with advanced disease or those refractory to other therapies.**
- **Intravenous epoprostenol is currently the only approved therapy for patients with PAH in functional class IV. Patients with severe PAH should not generally be considered candidates for oral or inhaled agents unless they refuse intravenous therapy or are not considered capable of managing the complex delivery system.**
- **A favourable effect of combination therapy has been observed in some studies, but not in others. Further research is necessary to convincingly demonstrate the superiority of combination therapy compared to monotherapy.**
- **Treatment of PAH with an oral agent costs between £4,500 and £20,000 per patient, per annum, excluding non-drug costs. Prostacyclin treatment costs between £31,000 and £137,000 per patient, per annum, excluding non-drug costs.**

BACKGROUND

Pulmonary arterial hypertension (PAH) is a severely disabling group of diseases characterised by a progressive increase in pulmonary vascular resistance (PVR) and impairment in activity tolerance, which in the absence of aggressive treatment may lead to right-heart failure and premature death.^{1,2} PAH is defined as a mean pulmonary artery pressure (mPAP) of ≥ 25 mmHg at rest and/or >30 mmHg on exertion, with a mean pulmonary capillary wedge pressure of ≤ 15 mmHg.^{1,3,4}

PAH is classified according to clinical and pathological features and by functional capacity. The 2003 third World Symposium on Pulmonary Hypertension in Venice established a revised clinical classification identifying five major groups and causes of pulmonary hypertension (Appendix 1).⁵ This revised system groups together the causes of pulmonary hypertension (PH) that share pathological features and illustrates the distinction between true PAH and other processes that can result in PH. PAH as defined above, represents group one within the revised classification and is further delineated according to whether it is an intrinsic process within the pulmonary vasculature, or secondary to other disease states.⁵ Idiopathic PAH (IPAH) occurs in the absence of diseases known to be associated with PAH, and replaces the previously used term 'primary pulmonary hypertension' (PPH).^{5,6} A genetic basis for PAH is suspected or documented in around 6% - 10% of patients with PAH.⁶ This autosomal dominant disease known as familial PAH (FPAH) is characterised by genetic anticipation, in which the age of disease presentation is increasingly younger with subsequent generations.^{6,7} PAH is increasingly recognised as being associated with other apparently disparate conditions such as connective tissue disease (CTD), congenital heart disease (CHD), and HIV infection, and this form is termed APAH.⁶

In addition to clinical classification, patients with PAH can also be classified according to their functional capacity. Traditionally patients are classified according to the New York Heart Association (NYHA) classification for patients with cardiac diseases, based on clinical severity and prognosis.^{8,9} The World Health Organisation (WHO) functional classification is an adaptation of the NYHA classification developed specifically for patients with PAH.^{8,10} The WHO and NYHA classifications are almost identical and are commonly referred to as the NYHA/WHO classification (Appendix 2).⁸

No formal studies have been done to determine the true incidence of PAH, but estimates suggest that approximately two to eight adult patients per million develop the disease annually,^{11,12} which approximates to between 100 and 350 new cases of PAH in England per year. The prevalence of PAH is difficult to determine but is estimated at between 15 and 26 cases per million of the population.^{11,12} In England in 2005-06, IPAH was responsible for 3,889 hospital admissions (all ages), and 4,386 finished consultant episodes, accounting for a total of 17,096 bed days.¹³

IPAH most commonly presents in the third decade of life in women and in the fourth decade in men, with a mean age upon diagnosis of 36 years and a female to male ratio of 1.7:1.¹⁴ Clinically, patients with PAH most commonly present with insidious breathlessness (dyspnoea), and fatigue.^{15,16} Symptoms are generally progressive and may be accompanied by anginal chest pains and syncope, often upon exertion.^{15,16} Syncope usually reflects a low cardiac output and is generally indicative of severe

disease.^{16,17} Many of these symptoms are non-specific, and are often not attributed to PAH at an initial consultation.^{15,17} Both non-invasive (e.g. echocardiography and cardiopulmonary function testing) and invasive tests (e.g. cardiac catheterisation and acute vasoreactivity testing) may be applied to establish a definitive diagnosis of PAH.^{4,17}

The natural history of IPAH is well described by the National Institutes of Health (NIH) registry, with a median life expectancy after diagnosis of 2.8 years without aggressive therapy.¹⁸ These data collected between 1981 and 1985, before the advent of disease-specific treatment options showed a one-year survival rate of 68%, and a five-year survival rate of 34%.¹⁸ However, significant advances in the assessment and treatment of PAH have considerably improved the prognosis of patients, with a more recent French registry study in 2002-2003 observing a one-year survival rate exceeding 88%.¹²

Treatment for PAH includes lifestyle modifications, conventional (non-specific) treatments, and disease-specific (targeted) treatments.⁶ The aims of treatment are to prevent disease progression, prevent pulmonary artery thrombosis, relieve the symptoms of PAH, improve exercise capacity, and ultimately prolong survival. Conventional therapies for PAH include anticoagulants, diuretics, digoxin and supplemental oxygen.¹⁹ Oral anticoagulants are indicated for the majority of patients with PAH.²⁰⁻²² The rationale for such therapy is based on the presence of well-established risk factors for thromboembolism, such as heart failure and sedentary lifestyle.^{19,22} In patients with decompensated heart failure, fluid retention can lead to increased central venous pressure, abdominal organ congestion, peripheral oedema, and in advanced cases ascites.¹⁹ Appropriate diuretic therapy aims to reduce afterload on the right side of the heart and treat the symptoms of heart failure and fluid overload.^{19,21} Since the depression of myocardial contractility seems to be one of the primary events in the progression of right-heart failure, short-term intravenous (i.v.) digoxin therapy may produce a modest increase in cardiac output in patients with IPAH.^{19,22} Hypoxemia is a potent vasoconstrictor which may contribute to the development and progression of PAH.²² The use of supplemental oxygen therapy to maintain arterial oxygen saturation >90% at all times is generally recommended.^{19,22}

Treatment of PAH with long-term oral calcium channel blockers (CCBs) is reserved for those patients who demonstrate a favourable response to acute vasodilator testing at the time of catheterization.²⁰⁻²² CCBs with a significant negative inotropic effect, such as verapamil should be avoided.^{1,6} Nifedipine and diltiazem are used most frequently, with the choice often based on the patients heart rate at baseline (relative bradycardia favouring nifedipine, and relative tachycardia favouring diltiazem).¹⁹ However, only around 10% to 15% of patients with IPAH respond initially to CCBs, and only half of these show a sustained clinical and haemodynamic response after one year of treatment.¹⁹⁻²² Patients with PAH who are not candidates for, or who have failed CCB therapy should be considered for long-term disease-specific therapy.^{1,6}

Significant advances in the treatment of PAH have occurred in the past five years with the development of a number of new targeted therapies. The purpose of this report is to review the efficacy, safety and place in treatment of current therapies

for the treatment of PAH. This report updates our previous reviews to include more recent data on the use of sildenafil, sitaxentan and ambrisentan in the treatment of PAH.

EFFICACY

Clinical trials performed in PAH have generally been small, relatively short-term studies, involving mainly patients with advanced disease. The six-minute walk test (6MWT) is the most widely used method of evaluating the response to therapy in PAH trials.^{2,4,8} The test, a simple measure of functional capacity, is safe and highly acceptable to patients, with highly reproducible results.² Predictors of survival in PAH include indicators of the severity of disease as assessed by measurement of haemodynamic characteristics (e.g. mPAP, right atrial pressure), and functional class. These variables are consistently used, along with time to clinical worsening, as measures of the effectiveness of interventions in the majority of clinical trials discussed in this document.

Three classes of drugs (prostacyclins, endothelin receptor antagonists (ETRA) and phosphodiesterase-5 (PDE-5) inhibitors), have shown benefit in the treatment of adults with PAH (NYHA/WHO functional class III and IV) in whom CCBs are inappropriate or no longer effective. Only those pivotal studies evaluating the efficacy, safety and place in therapy of these agents are presented.

PROSTACYCLINS

Epoprostenol

Epoprostenol (Flolan[®], GlaxoSmithKline UK), a naturally occurring prostacyclin produced by vascular endothelium, is a potent vasodilator and inhibitor of platelet aggregation.²³ It is licensed for the i.v. treatment of PPH in NYHA/WHO class III and IV patients who do not respond adequately to conventional therapy.²³

A pivotal 12-week randomized, multi-centre, open-label trial compared the efficacy of continuous i.v. epoprostenol (2 ng/kg/min and increased by increments of 2 ng/kg/min every 15 min) plus conventional therapy (anticoagulants, vasodilators, diuretics, digoxin, and supplemental oxygen) with conventional therapy alone in 81 NYHA functional class III or IV patients with PPH.²⁴ The primary endpoint was change in 6MWT from baseline. Secondary endpoints included survival and quality of life. Baseline haemodynamics were established by right-heart catheterisation and re-evaluated at the end of the study. The initial dose in patients treated with long-term infusion of epoprostenol was 5.3 ± 0.5 ng/kg/min; the dose was increased to 9.2 ± 0.8 ng/kg/min by the end of the study. After 12 weeks of treatment, the group given epoprostenol showed significant improvement in the 6MWT (+31 m, $p < 0.002$) compared to conventional therapy alone (-29 m). Epoprostenol treatment was also associated with a significant reduction in mPAP ($p < 0.002$) and pulmonary vascular resistance (PVR, $p < 0.001$), and indices of quality of life were improved only in the epoprostenol group ($p < 0.01$).

Two large long-term observational studies have demonstrated an improvement in survival in patients with PAH treated with epoprostenol compared to either historical control subjects or predicted survival based on the National Institutes of Health (NIH) registry equation. McLaughlin et al, observed 162 NYHA class III or IV patients with PPH despite optimal medical therapy.²⁵ The survival rates for patients treated with epoprostenol at one, two and three years were 88%, 76%, and 63% compared with predicted survival rates of 59%, 46%, and 35% respectively, using the NIH equation ($p < 0.001$, at all time points). In a second similar study Sitbon et al observed 178 NYHA class III or IV patients with PPH despite optimal medical therapy. At one, two, three, and five years, overall survival rates were 85%, 70%, 63%, and 55% compared with 58%, 43%, 33%, and 28% respectively, for historical controls ($p < 0.0001$).²⁶

Iloprost

Iloprost (Ventavis[®] ▼, Bayer) is a synthetic prostacyclin analogue that is administered via inhalation using a nebuliser.²⁷ Nebulised iloprost is licensed for the treatment of patients with PPH in NYHA/WHO class III, to improve exercise capacity and symptoms.²⁷ Intravenously administered iloprost is not currently licensed for the treatment of PAH in the UK and therefore has not been included in this report.

The efficacy of iloprost for the treatment of adults with PAH has been evaluated in a single, pivotal, randomised, double-blind, multi-centre, placebo-controlled trial. The Aerosolised Iloprost Randomised (AIR) study enrolled 203 NYHA functional class III or IV patients with stable PAH that was either primary or selected forms of secondary.^{28,29} Participants were randomised to placebo ($n=102$) or inhaled iloprost 2.5 or 5.0 micrograms six or nine times daily ($n=101$). Conventional PAH therapies, including anticoagulants, vasodilators, diuretics, digoxin, and/or supplemental oxygen, were continued in each group. CCB doses had to have been constant for at least six weeks prior to study entry. Patients receiving prostacyclin, investigational drugs or beta-blockers were excluded. The primary endpoint was a composite of improvement from baseline in 6MWT ($\geq 10\%$), plus an improvement in at least one NYHA function class versus baseline, and no deterioration of PAH or death at any time during the 12-week study. Secondary endpoints included changes in the 6MWT values, NYHA functional class, Mahler Dyspnoea Index scores, cardiopulmonary haemodynamics, quality of life and clinical deterioration. At week 12, the primary composite endpoint was met by 16.8% of patients receiving iloprost (median inhaled dose 30 micrograms per day), compared to 4.9% of the placebo group ($p=0.007$). The absolute change in the 6MWT was significantly larger in the iloprost group compared to placebo (+36.4 m, $p=0.004$). Significantly more patients in the iloprost group (23.8%) had an improvement in one NYHA functional class compared to placebo (12.7%, $p=0.03$). The percentage of patients with deterioration in functional class did not differ significantly between the groups. One patient died in the iloprost group compared to four in the placebo group ($p=0.37$). The criteria for clinical deterioration were met in 4.9% of patients receiving iloprost compared to 8.8% of patients receiving placebo ($p=0.41$). There were significant improvements with iloprost compared to placebo in the Mahler Dyspnoea Index scores ($p=0.015$) and in one quality of life measure (EuroQol visual-analogue scale, $p=0.026$). No significant difference was observed in any other endpoint.

The unpublished AIR-2 study, an open-label, multicentre, randomised, parallel-group trial compared the addition of inhaled iloprost (2.8 micrograms per inhalation) to conventional therapy with conventional therapy alone (excluding prostacyclins and ETRAs).²⁹⁻³¹ Inclusion and exclusion criteria were similar to the AIR study. A total of 63 patients with PPH or secondary PH in NYHA class II (33%), III (48%) or IV (19%) received treatment for three months, at which point all patients (excluding those who had discontinued treatment due to adverse effects or deterioration) continued on iloprost in a 24-month open-label extension study. Although primarily the study was designed to evaluate safety, a composite response criterion was specified to analyse efficacy. Patients were classified as responders if they fulfilled each of the following criteria: an improvement in at least one NYHA class and at least a 10% increase in the 6MWT in the absence of death. At week-12, significantly more patients in the iloprost group compared with the control group had reached the primary efficacy endpoint (4 vs. 0, $p=0.046$). When the components of the primary endpoint were analysed separately, iloprost was not associated with a statistically significant improvement in NYHA class or 6MWT compared with placebo. Among the 52 patients who continued into the long-term phase 36 completed at least 630 days of therapy. All four patients who had met the composite clinical response criterion continued to do so up to 24 months and five patients from the control group also met the criterion on treatment with iloprost.

Combination therapy – iloprost and bosentan

Two studies have assessed the safety and efficacy of combining inhaled iloprost with bosentan in patients with PAH. In the first (COMBI) study, 40 patients with IPAH in NYHA functional class III were randomised to receive either bosentan alone ($n=21$) or bosentan plus inhaled iloprost ($n=19$) for a 12-week period.³² The trial was stopped early after no apparent benefit was observed in the primary endpoint, change in 6MWT (mean changes +1 m and -9 m in the control and combination group, respectively). None of the secondary endpoints including functional class, peak oxygen uptake, and time to clinical worsening differed significantly between groups. In the second (STEP) study, 67 patients with PAH in NYHA class III receiving bosentan therapy were randomized to receive additional inhaled iloprost ($n=34$) or placebo ($n=33$).³³ Efficacy endpoints included change from baseline in 6MWT, functional class, haemodynamic parameters, and time to clinical worsening. At week-12, patients receiving iloprost had a mean post-inhalation increase in 6MWT of +30 m compared to an increase of +4 m in those receiving placebo ($p=0.051$). NYHA functional status improved by one class in 34% of iloprost versus 6% of placebo patients ($p=0.002$). Iloprost delayed the time to clinical worsening ($p=0.0219$), and significantly improved post-inhalation mPAP ($p<0.001$) and PVR ($p<0.007$). However, changes in haemodynamics did not reach significance when measured pre-inhalation.

ENDOTHELIN ANTAGONISTS

Bosentan

Bosentan (Tracleer[®]▼, Actelion Pharmaceuticals) is an oral, dual ETRA with affinity for both endothelin A and B receptors.³⁴ It is licensed for the treatment of PAH to

improve exercise capacity and symptoms in patients in NYHA/WHO functional class II and III.³⁴ The efficacy of bosentan monotherapy for the treatment of adults with PAH has been evaluated in three, randomised, double-blind, multi-centre, placebo-controlled trials:³⁵⁻³⁷

The first study enrolled 32 patients in WHO functional class III with symptomatic IPAH or PAH associated with scleroderma.³⁵ Participants were randomised to placebo, (n=11) or bosentan (62.5 mg twice daily for four weeks then a maintenance dose of 125 mg twice daily, n=21). Conventional PAH therapies, including anticoagulants, vasodilators, diuretics, digoxin, and supplemental oxygen, were continued in each group. Patients receiving long-term epoprostenol were excluded. The primary endpoint was change in 6MWT at 12 weeks. Secondary endpoints included change in cardiopulmonary haemodynamics, Borg dyspnoea index, NYHA functional status, and time to clinical worsening. At week 12, the placebo-corrected increase in the 6MWT with bosentan compared with baseline was 76 m (p=0.02). Patients taking bosentan also showed significant improvements in pulmonary haemodynamics (p<0.05), NYHA functional class (p=0.019), and time to clinical worsening (p=0.033) compared with those on placebo. The improvement in 6MWT with bosentan compared to placebo was maintained for at least 20 weeks. In a follow-up study, 29 of the patients received open-label bosentan for an additional year.³⁸ At six months, patients continuing with bosentan maintained the improvement in 6MWT, and patients starting bosentan improved their 6MWT by a mean of +45 m.

The pivotal BREATHE-1 trial (Bosentan Randomised trial of Endothelin antagonist THERapy for pulmonary hypertension), enrolled 213 patients in NYHA functional class III or IV with PPH or IPAH associated with CTD.³⁶ Participants were randomised to placebo, (n=69) or bosentan 125 mg (n=74) or 250 mg (n=70) twice daily for 16 weeks. All bosentan patients received 62.5 mg twice a day for four weeks and were then up-titrated to the target dose. Conventional PAH therapies, including anticoagulants, vasodilators, diuretics, digoxin, and supplemental oxygen, were continued in each group. Patients using i.v. epoprostenol within three months were excluded. The primary endpoint was change in 6MWT at 16 weeks. Secondary end points included the change in Borg dyspnoea index, change in functional status and time to clinical worsening. At week 16, the placebo-corrected increase in the 6MWT for bosentan 125 mg twice daily or bosentan 250 mg twice daily was +35 m (p<0.01) or +54 m (p<0.001) respectively. For the combined bosentan groups, the placebo-corrected increase in walking distance was +44 m (p<0.001). There was no significant difference between the two bosentan groups (p=0.18). Time to clinical worsening was significantly increased with bosentan compared to placebo (p<0.002). There were no significant differences in the change in Borg dyspnoea index or change in functional status between the bosentan and placebo groups.

A retrospective subgroup analysis of 169 patients with PPH included in these two studies suggested that survival rates of patients taking bosentan were significantly greater than the predicted survival rates (using the National Institutes of Health PPH equation).³⁹ At 12 and 24 months, the estimated survival rates of patients on bosentan were 96% and 89%, respectively, compared with predicted survival rates of 69% and 57%. However, only 85% of patients were still on bosentan monotherapy at year one and 70% at two years.

The EARLY trial enrolled patients in WHO functional class II with mildly symptomatic IPAH, FPAH, or PAH associated with HIV infection, anorexigen use, CHD, CTD or auto-immune disease.³⁷ In total 185 patients were randomly assigned to receive bosentan (n=93) or placebo (n=92) for six months. All bosentan patients received 62.5 mg twice daily for four weeks, up-titrating to 125 mg twice daily (or remaining on 62.5 mg twice daily if bodyweight <40 kg). Conventional PAH therapies, including anticoagulants and CCBs, were continued in each group. Patients using approved PAH therapies (e.g. prostacyclin or an ETRA) were excluded. Because sildenafil received approval for the treatment of PAH during the period this study was ongoing, the protocol was amended to allow its use. The primary endpoints were changes from baseline in PVR at rest and 6MWT at six months. Secondary endpoints included time to clinical worsening, change in functional status and Borg dyspnoea index. The primary analysis set for PVR consisted of 168 patients (bosentan n=80 and placebo n=88). At month six, PVR was 83.2% of the baseline value in the bosentan group and 107.5% of baseline in the placebo group (treatment effect -22.6% p<0.0001). A similar treatment effect was seen in patients with or without concomitant sildenafil at baseline (-20.4%; p=0.047 and -23.1%; p<0.0001, respectively). The primary analysis set for 6MWT consisted of 177 patients (bosentan n=86 and placebo n=91). Mean 6MWT did not improve significantly compared with placebo, (+19 m, p=0.08). Bosentan treatment was associated with a significant delay in time to clinical worsening and a lower incidence of deterioration in functional class compared to placebo (p=0.011 and p=0.029, respectively). No significant changes in Borg dyspnoea index were seen.

Combination therapy – bosentan and epoprostenol

The combination of bosentan and i.v. epoprostenol has been investigated in a randomised, double-blind, placebo-controlled trial (BREATHE-2).⁴⁰ A total of 33 patients in NYHA functional class III or IV started epoprostenol treatment at 2 ng/kg/min (increased at two-weekly intervals to reach a target dose of 1216 ng/kg/min). Two days later they were randomised to receive bosentan (65 mg twice daily for four weeks followed by 125 mg twice daily) or placebo. Patients were excluded if they had interstitial lung disease or had started or stopped any PAH treatment within one month of screening. The primary endpoint was the change from baseline in total pulmonary resistance at 16 weeks. Secondary endpoints included 6MWT and change in functional class. At week 16, there was no significant difference between the two treatment groups, with improved haemodynamics, 6MWT and functional class observed in both groups.

Sitaxentan

Sitaxentan (Thelin®▼, Encysive Pharmaceuticals) is an orally active selective endothelin-A receptor antagonist.⁴¹ It is licensed for the treatment of PAH to improve exercise capacity and symptoms in patients in NYHA/WHO functional class III.⁴¹ The efficacy of sitaxentan for the treatment of adults with PAH has been evaluated in three pivotal, randomised, double-blind, multi-centre, placebo-controlled trials: STRIDE-1, STRIDE-2 and STRIDE-4.⁴²⁻⁴⁸

The Sitaxsentan to Relieve Impaired Exercise-1 (STRIDE-1) study enrolled 178 NYHA functional class II-IV patients with symptomatic PAH that was either idiopathic, associated with CTD or CHD.^{42,48} Participants were randomised to placebo, (n=60) sitaxentan 100 mg (n=55) or 300 mg (n=63) daily for 12 weeks. Conventional PAH therapies, including anticoagulants, vasodilators, diuretics, digoxin, and supplemental oxygen were continued in each group. Patients using non-conventional PAH therapies (e.g. prostacyclin or an ETRA) were excluded. The primary endpoint was change in peak oxygen consumption (VO_2) with cardiopulmonary exercise testing. Secondary endpoints included changes in the 6MWT, NYHA functional class, cardiopulmonary haemodynamics, and time to clinical worsening. At week 12, patients receiving 300 mg sitaxentan, but not 100 mg, demonstrated a significant improvement in peak VO_2 consumption compared with placebo (+3.1%, $p<0.01$). However the measurement of peak VO_2 as a reliable endpoint in multicentre trials of PAH has been questioned.⁴⁹ None of the other endpoints derived from cardiopulmonary exercise testing were met. Both doses of sitaxentan were associated with significant improvements in the 6MWT compared to placebo (100 mg +35 m, and 300 mg +33 m, both $p<0.01$). NYHA functional class, cardiac index, and PVR also improved compared to placebo ($p<0.02$ for each parameter at both doses). There were no clinically meaningful differences among the groups in the time to clinical worsening, although this may have been due to the high prevalence of patients with mild to moderate disease in the study. Traditionally, clinical trials of PAH have limited enrolment to functional class III and IV patients. In a post-hoc analysis of STRIDE-1 including only those 70 patients who met these criteria (class III and IV, excluding CHD) sitaxentan treatment was associated with a significant improvement in 6MWT compared to placebo (+65 m, $p=0.0002$).^{45,46}

Patients completing STRIDE-1 were eligible to continue in a blinded extension study, (STRIDE-1X) and received sitaxentan 100 mg (n=79) or 300 mg (n=91) daily.^{49,50} In all patients receiving sitaxentan in both studies (mean treatment duration 26 weeks) improvement of at least one NYHA functional class was demonstrated in 42 patients (53%) and 40 patients (44%), respectively. Although most of the patients who improved did so in the first 12 weeks of treatment, none of those that deteriorated had previously improved. The favourable efficacy and safety profile of 100 mg supports its selection as the optimum therapeutic dose.

The STRIDE-2 study enrolled 247 WHO functional class II, III or IV patients with symptomatic PAH that was either idiopathic, or associated with CTD or CHD.^{43,48} Participants were randomised to placebo, (n=62) sitaxentan 50 mg (n=62) or 100 mg (n=61) daily; or open-label bosentan titrated to 125 mg twice daily (n=60). The bosentan arm was included for observation purposes only, as the drug was only available on a named patient basis and therefore blinded drug supplies were not available; however, efficacy assessments were third-party blind. Conventional PAH therapies were continued in each group. Patients using non-conventional PAH therapies were excluded. The primary endpoint was change in 6MWT from baseline. Secondary endpoints included changes in WHO functional class, time to clinical worsening, and change in Borg dyspnoea score. At week 18, the 6MWT improved significantly in the sitaxentan 100 mg and open-label bosentan 125 mg groups (+31.4 m; $p=0.03$ and +29.5 m; $p=0.05$, respectively) compared with placebo, but not for those in the sitaxentan 50 mg group (+24.2 m; $p=0.07$). The change from

baseline in WHO functional class was significantly better in the sitaxentan 100 mg group compared with placebo ($p=0.04$). No significant improvement was seen in WHO functional class versus placebo in either the sitaxentan 50 mg or the open-label bosentan group. No significant differences in time to clinical worsening or Borg dyspnoea scores were observed between any of the treatment groups compared to placebo.

Patients completing STRIDE-2 were eligible to enrol in STRIDE-2X, a one-year open-label extension study.^{41,47} A total of 145 patients received 100 mg sitaxentan. In this total population, Kaplan-Meier estimates of survival were 96% after one year of sitaxentan treatment. However, this result may have been influenced by the initiation of new or additional PAH therapies, which occurred in 10% and 13% of patients, respectively.

The STRIDE-4 study was designed to test the relative efficacy of 50 mg versus 100 mg sitaxentan.^{44,48} In total, 98 WHO functional class II-IV patients were randomised to placebo, ($n=34$) sitaxentan 50 mg ($n=32$) or 100 mg ($n=32$) daily. The primary endpoint was change in 6MWT from baseline. Due to a disproportionate enrolment of functional class II patients (61%) the study was underpowered to detect a between-group difference versus placebo in the primary endpoint. However, the improvement in exercise capacity was significantly greater in the sitaxentan 100 mg group compared to the 50 mg group (58 m vs. 22 m, $p=0.014$). No patients receiving sitaxentan 100 mg deteriorated in WHO functional class versus 12% of patients receiving placebo and 6% of those receiving sitaxentan 50 mg (p value not given). Time to clinical worsening was not statistically different in either sitaxentan group compared with placebo.

Ambrisentan

Ambrisentan (Volibris®▼, GlaxoSmithKline) is an orally active selective ETRA.⁵¹ It is licensed for the treatment of PAH to improve exercise capacity in patients in NYHA/WHO functional class II and III.⁵¹ The efficacy of ambrisentan for the treatment of adults with PAH has been evaluated in two pivotal, randomised, double-blind, multi-centre, placebo-controlled trials: ARIES-1 and ARIES-2.^{52,53}

ARIES-1 and ARIES-2 were identical in design except for the doses of ambrisentan studied and involved a total of 394 WHO functional class I-IV patients with PAH (idiopathic, associated with CTD, anorexigen or HIV infection).^{52,53} Conventional PAH therapies, including anticoagulants, vasodilators, diuretics and digoxin were continued in each group.⁵¹ Patients using non-conventional PAH therapies (prostacyclin, ETAs and PDE-5 inhibitors) were excluded.⁵³ The primary endpoint was change in 6MWT from baseline at week 12 compared to placebo. Secondary endpoints included time to clinical worsening, change in WHO functional class, the SF-36 health survey, and Borg dyspnoea score. All patients who completed either study were eligible to enter a long-term open-label extension study (ARIES-E).

In ARIES-1, participants were randomised to placebo ($n=67$), ambrisentan 5 mg ($n=67$) or 10 mg ($n=68$) daily for 12 weeks.^{52,53} The mean placebo subtracted change from baseline in the 6MWT at week 12 was +51 m ($p<0.001$) in the 10 mg ambrisentan group and +31m ($p=0.008$) in the 5 mg group. A significant improvement

in the Borg dyspnoea score was also observed in the 10 mg ambrisentan group compared to placebo ($p=0.002$). No significant improvements in functional class,⁵³ time to clinical worsening or the SF-36 survey were observed for either treatment group alone compared to placebo.

In ARIES-2, participants were randomised to placebo ($n=65$), ambrisentan 2.5 mg ($n=64$) or 5 mg ($n=63$) daily for 12 weeks.^{52,53} The placebo-subtracted change from baseline in the 6MWT at week 12 was +59 m ($p<0.001$) in the 5 mg ambrisentan group and +32 m ($p=0.022$) in the 2.5 mg group. Significant improvements in time to clinical worsening were observed for both the 5 mg group ($p=0.008$) and the 2.5 mg group ($p<0.005$). Improvements compared to placebo were also observed for both groups in the SF-36 survey ($p=0.040$ and $p=0.005$, respectively) and the Borg dyspnoea score ($p=0.040$ and $p=0.046$, respectively). No significant improvements in functional class were observed for either group.

ARIES-E, an ongoing long-term extension study of the ARIES-1 and -2 trials, demonstrated that the improvements in the 6MWT observed during the first 12 weeks of ambrisentan treatment were sustained for at least 48 weeks in an integrated analysis of 383 patients who received at least one dose of ambrisentan.⁵⁴ Improvements in WHO functional class and Borg dyspnoea index were also maintained with long-term treatment. One-year survival was comparable for the 2.5 mg, 5 mg and 10 mg ambrisentan groups (range 94.7% to 96.8%). The mean change from baseline in 6MWT for the 280 patients receiving ambrisentan monotherapy at week 48 for all doses combined was +39 m.⁵²

PHOSPHODIESTERASE INHIBITORS

Sildenafil

Sildenafil (Revatio®▼, Pfizer Ltd) is an oral PDE-5 inhibitor.⁵⁵ It is licensed for the treatment of PAH to improve exercise capacity in patients in NYHA/WHO functional class III.⁵⁵ The efficacy of sildenafil monotherapy for the treatment of adults with PAH has been evaluated in a single pivotal, randomised, double-blind, multi-centre, placebo-controlled trial.^{56,57} The Sildenafil Use in Pulmonary Hypertension (SUPER1) study enrolled 278 NYHA functional class I-IV patients with symptomatic PAH that was primary, associated with CTD or following repair of congenital heart defects.⁵⁶ Participants were randomised to placebo ($n=70$), sildenafil 20 mg ($n=69$), 40 mg ($n=67$) or 80 mg ($n=71$) three times daily. Conventional PAH therapies, including anticoagulants, vasodilators, diuretics, digoxin, and supplemental oxygen, were continued in each group. Patients using non-conventional PAH therapies (i.e. prostacyclin or an ETRA) and arginine supplementation were excluded. The primary endpoint was change in 6MWT from baseline to week 12. Secondary endpoints included changes in mPAP, WHO functional class, Borg dyspnoea score, and time to clinical worsening. At week 12, a statistically significant increase in 6MWT was observed in all three treatment groups compared to placebo. The placebo subtracted increase in 6MWT were +45 m, +46 m and +50 m (all $p<0.001$) for sildenafil 20 mg, 40 mg and 80 mg, respectively). There was no evidence of a dose-response relationship associated with the primary endpoint. Patients on all sildenafil doses achieved statistically significant reductions in mPAP compared to

those on placebo. Doses of 20 mg, 40 mg, and 80 mg produced placebo-corrected decreases in mPAP of -2.7 mmHg, -3.2 mmHg, and -5.3 mmHg, respectively. There was some evidence of a dose-dependent decrease in mPAP.⁵⁷ A significantly higher percentage of patients in each sildenafil group showed an improvement of at least one functional class compared to placebo ($p < 0.004$ for all). Time to clinical worsening and change in Borg dyspnoea score did not differ significantly from placebo in any sildenafil group.

All patients who completed the SUPER1 study were eligible to enter the long-term extension study (SUPER-2) in which patients were titrated to sildenafil 80 mg three times daily if tolerated ($n = 259$).^{56,57} Conventional PAH therapy, except bosentan was permitted. Subjects previously assigned to placebo reached a dose of 80 mg three times daily at week 24, and showed a mean increase from baseline in 6MWT of +46 m, which is comparable to the improvement seen in the sildenafil groups from baseline to week 12 in the SUPER-1 study. The mean increase in 6MWT at week 24 was approximately +50 m in those previously assigned to sildenafil and receiving 80 mg three times daily. However, in the absence of a control group these results should be interpreted with caution.

Comparator study – sildenafil vs. bosentan

The SERAPH study, a randomised, double-blind, controlled trial compared the effects of sildenafil and bosentan in 26 patients with PAH in functional class III.⁵⁸ Participants were randomised to receive sildenafil (50 mg twice daily for four weeks, then 50 mg three times daily), or bosentan (62.5 mg twice daily for four weeks, then 125 mg twice daily). All patients were symptomatic despite conventional therapy with diuretics, digoxin and anticoagulants. Patients with elevated liver enzymes and those previously receiving sildenafil or bosentan therapy were excluded. The primary endpoint was change in right ventricular (RV) mass from baseline. Secondary endpoints included change in 6MWT, cardiac index, Borg dyspnoea score and quality of life. At week 16 there were no significant differences between the two treatment groups for any endpoint when analysed by intention-to-treat.

Combination therapy – sildenafil and bosentan

The combination of sildenafil and bosentan has been investigated in one uncontrolled case series.⁵⁹ A total of nine patients with severe IPAH in functional class III or IV, in whom bosentan (62.5 mg twice daily for four weeks, then 125 mg twice daily) caused a transient clinical improvement, followed by a decline in exercise tolerance, received additional therapy with sildenafil (25 mg to 50 mg three times daily). Follow-up measurements included 6MWT and cardiopulmonary exercise testing. Three months after sildenafil was added to bosentan significant improvements in both 6MWT ($p = 0.007$) and peak oxygen uptake ($p = 0.006$) were observed compared to baseline values before the addition of sildenafil. Functional class improved in three patients, and six showed no deterioration. The effects on exercise capacity were maintained throughout the follow-up period of up to 12 months.

Combination therapy – sildenafil and epoprostenol

Two studies have assessed the safety and efficacy of combining sildenafil and i.v. epoprostenol in patients with PAH.⁶⁰⁻⁶² In the PACES study, 267 patients with PAH in functional Class I to IV stabilised on i.v. epoprostenol were randomised to receive either placebo or sildenafil (20 mg three times daily titrated to 40 mg and 80 mg three times daily at four-week intervals).^{60,61} The primary efficacy endpoint was the change in 6MWT from baseline. Secondary endpoints included change from baseline in mPAP, time to clinical worsening and Borg dyspnoea score. At week 16 the 6MWT increased by +26 m ($p < 0.001$). Combination therapy also decreased mPAP to a greater extent (-3.9 mm Hg) than epoprostenol alone ($p = 0.0001$). Time to clinical worsening was significantly longer in patients on combination therapy ($p = 0.012$), and no patients died when treated with combination therapy compared to seven deaths in the epoprostenol group. There was no effect on Borg dyspnoea score. In a second uncontrolled study the addition of long-term sildenafil (up to 200 mg/day for five months) improved mPAP and 6MWT in three patients receiving longterm i.v. epoprostenol therapy.⁶²

Combination therapy – sildenafil and iloprost

One uncontrolled study assessed the safety and efficacy of combining sildenafil and inhaled iloprost in patients with PAH.⁶³ The aim of the study was to investigate the impact of adjunct sildenafil therapy on exercise capacity and haemodynamic parameters in patients with PAH in functional class III or IV, who were deteriorating despite ongoing treatment with iloprost. A total of 14 patients received adjunct sildenafil (25 mg to 50 mg, three times daily), while leaving the iloprost inhalation regimen unchanged during the period of combination. The mean interval between the onset of long-term iloprost inhalation therapy and the onset of adjunct sildenafil therapy due to clinical deterioration was 18 ± 4 months. The addition of sildenafil was associated with a significant and persistent improvement in 6MWT compared with pre-sildenafil values ($p = 0.002$, $p = 0.014$, and $p = 0.002$ after three, six and 9 - 12 months, respectively). A favourable change in functional class was observed in most patients, and PVR decreased significantly ($p = 0.036$) after three months treatment in all patients compared with pre-sildenafil values.

ADVERSE EFFECTS**PROSTACYCLINS**

Common adverse effects of treatment with prostacyclins include jaw pain, diarrhoea, abdominal pain, headache, flushing, arthralgia and muscle pain. Ascites and pulmonary oedema may occur as these drugs increase vascular permeability.

Epoprostenol

Adverse events reported in clinical trials included: jaw pain, flushing, nausea, vomiting, headache and sepsis (very common 10%); anxiety, abdominal pain, decreased platelet count, tachycardia and bradycardia (common 1% and <10%).²³

Serious adverse events were most often due to delivery system complications.²⁴⁻²⁶ The reported catheter-related sepsis rate was 0.14 to 0.19 per patient year.^{25,26} Malfunction of the delivery system has also been reported, with one patient death directly attributed to interruption of the epoprostenol infusion.^{24,25}

Iloprost

The overall proportion of subjects with common adverse events in the pivotal AIR study was similar in the iloprost and placebo groups (90% vs. 89%), and the total number of patients who had serious adverse events did not differ significantly between the groups (28% vs. 25%).²⁸ The most commonly reported adverse events that occurred more frequently with iloprost than with placebo were flushing (27% vs. 9%, $p=0.001$), jaw pain (12% vs. 3%, $p=0.02$) and cough (39% vs. 26%, $p=0.05$). Other adverse events included: headache, influenza-like syndrome, peripheral oedema, nausea, hypotension, diarrhoea, and vertigo. The total number of syncopal events in each group were similar, but these events were more often considered serious in the iloprost group (5% vs. 0%, $p=0.03$). In the long-term follow-up (AIR-2) study, the commonly reported adverse events were similar to those reported in the pivotal study.³¹

ENDOTHELIN ANTAGONISTS

ETRAAs as a class have been associated with dose-related liver function abnormalities.⁵³

Bosentan

In the placebo-controlled studies in patients with PAH in functional class III or IV, the adverse events that occurred more frequently with bosentan than placebo (in $\geq 3\%$ of bosentan-treated patients) were nasopharyngitis (11% vs. 8%), flushing (9% vs. 5%), abnormal hepatic function (8% vs. 3%), leg oedema (8% vs. 5%), hypotension (7% vs. 4%), palpitations (5% vs. 1%), dyspepsia (7% vs. 0%), fatigue (4% vs. 1%) and pruritis (4% vs. 0%).³⁴ Anaemia, gastro-oesophageal reflux disease and rectal haemorrhage were also reported more often in patients receiving bosentan than placebo (all 2.4% vs. 0%).³⁴ Treatment withdrawals due to adverse events were more common in placebo-treated patients than those on bosentan (10% vs. 5.5%, respectively).³⁴ In patients with mildly symptomatic PAH (functional class II), adverse events were comparable to those observed in the placebo-controlled studies described above.³⁷

Bosentan was associated with dose-related increases in aminotransferases, which mainly appeared within the first 26 weeks of treatment and were largely asymptomatic.³⁴ The incidence of elevated aminotransferase levels >3 x the upper limit of normal (ULN), were 11.6% and 14.3% for patients receiving 125 mg and 250 mg twice daily, respectively. Eight-fold increases were seen in 2.1% of patients receiving bosentan 125 mg twice daily, and 7.1% of patients on 250 mg twice daily. In patients with mildly symptomatic PAH the incidence of elevated aminotransferase levels >3 x ULN, was 13% for patients receiving bosentan and 2% for placebo.³⁷ In all cases, levels returned to pre-treatment levels without sequelae either spontaneously

or after dose reduction/treatment withdrawal.^{34,37} Clinically relevant decreases in haemoglobin occurred in 3.0% of bosentan-treated patients compared to 1.3% receiving placebo.³⁴

Sitaxentan

In the three placebo-controlled studies in patients with PAH (STRIDE-1, -2 and 4), at least one treatment-emergent adverse event (AE) was experienced by comparably high proportions of all treatment groups (all sitaxentan 91%, sitaxentan 100 mg 92%, placebo 92%, and bosentan 89%).⁴⁸ The most commonly reported adverse events that occurred in >10% of patients receiving sitaxentan 100 mg included headache (28%), peripheral oedema (21%), nausea (15%), upper respiratory tract infection (15%), dizziness (13%), nasopharyngitis (13%), nasal congestion (13%) and insomnia (13%).⁴⁸ The adverse events that occurred more frequently with sitaxentan 100 mg (difference \geq 5%) than placebo were peripheral oedema (21% vs. 16%), insomnia (13% vs. 6%), nasopharyngitis (13% vs. 7%), nasal congestion (13% vs. 6%), upper respiratory tract infection (15% vs. 8%) and epistaxis (8% vs. 3%).⁴⁸ A marked decrease in haemoglobin (>15% decrease from baseline and below the lower limit of normal) was observed in 7% of patients treated with sitaxentan compared to 3% receiving placebo.⁴⁸ Adverse events that occurred more frequently (difference \geq 5%) with sitaxentan 100 mg than bosentan were vomiting (5% vs. 0%), muscle cramp (7% vs. 0%), headache (28% vs. 20%), insomnia (13% vs. 0%), cough (5% vs. 13%), dyspnoea (7% vs. 15%) and pulmonary hypertension (1% vs. 7%).⁴⁸ Overall, across all three studies, the incidence of elevated aminotransferase levels (>3 x ULN) was 2% for sitaxentan 100 mg and 5% for placebo.⁴⁷

Ambrisentan

In ARIES-1 and -2, a total of 261 patients received ambrisentan at doses of 2.5 mg, 5 mg or 10 mg once daily and 132 patients received placebo.⁶⁴ The adverse events that occurred in >3% of patients receiving ambrisentan and more frequently than with placebo included (placebo-adjusted frequency): peripheral oedema (6%), nasal congestion (4%), sinusitis (3%), flushing (3%), palpitations (3%), nasopharyngitis (2%), abdominal pain (2%), constipation (2%), dyspnoea (1%) and headache (1%).⁵¹ The overall frequency of discontinuation due to adverse events other than those related to PAH were similar for ambrisentan (2%) and placebo (2%).⁶⁴ The incidence of patients with serious adverse events other than those related to PAH were also similar in the two groups (7% vs. 5%, respectively).⁶⁴ Ambrisentan was associated with aminotransferase (ALT and AST) elevations >3 x ULN in 0.8% of patients in 12-week trials and 2.8% of patients in long-term open label trials out to one year. One case of aminotransferase >3 x ULN was accompanied by bilirubin elevations >2 x ULN.⁶⁴

PHOSPHODIESTERASE INHIBITORS

Sildenafil

The overall proportions of subjects with common adverse events in the pivotal SUPER-1 study were similar across all treatment groups including placebo (~90%),

which was also true for the proportion of subjects with serious adverse events (~17%).⁵⁷ The most common adverse events ($\geq 3\%$) reported with sildenafil and more frequently than with placebo included: headache (46% vs. 39%), flushing (12% vs. 4%), back pain (12% vs. 11%), dyspepsia (11% vs. 7%), diarrhoea (10% vs. 6%), limb pain (10% vs. 6%) and myalgia (9% vs. 4%). Several of these common adverse events are already known to occur with sildenafil treatment in male erectile dysfunction (MED), but rates are generally lower in MED patients receiving 25-100 mg (as required) compared to these chronically treated PAH patients on higher daily doses. The overall frequency of discontinuation in the sildenafil-treated patients at the recommended dose of 20 mg three times daily was low and the same as with placebo (2.9%). No deaths during the study were adjudged by the investigators to be causally related to the study treatment. In the SUPER-2 extension study, the incidence of adverse events (normalised to sildenafil exposure) were comparable to those observed in the SUPER-1 study. No cases of priapism were noted in either study.

ARRANGEMENTS FOR PRESCRIBING

In 2001 the National Specialist Commissioning Advisory Group (NSCAG, now known as the National Commissioning Group (NCG)) designated a specialist service for the treatment of PH.⁶⁵ There are six designated centres in England: Newcastle (Freeman Hospital), Sheffield (Royal Hallamshire Hospital), Cambridge (Papworth Hospital), and London (Royal Brompton, Hammersmith and Royal Free Hospitals). In April 2007, a service for children was designated and commissioned by NSCAG, with a single designated centre in London (Great Ormond Street Hospital).⁶⁶ Treatment for PH should only be initiated by specialists based at these centres. Unlike most NCG services, the service costs for the treatment of PAH for adults continue to be funded by the NHS. Primary Care trusts (PCTs) are required to commission the service through formal collaborative arrangements established by the Specialist Commissioning Group (SCG) responsible for their area. Funding is provided on an individual named patient basis by PCTs to whom applications must be made by a designated centre. For children, the NCG funds both the service and the drug therapies.⁶⁶

DOSAGE, ADMINISTRATION AND COST

PROSTACYCLINS

Epoprostenol

Epoprostenol should only be initiated and monitored by a physician experienced in the treatment of PAH. Epoprostenol is administered as a continuous infusion via a central venous catheter.²³ A short-term dose-ranging procedure administered via either a peripheral or central venous line is required to determine the long-term infusion rate. The infusion rate is initiated at 2 ng/kg/min and increased by

increments of 2 ng/kg/min every 15 min or longer until maximum haemodynamic benefit is obtained or dose-limiting adverse effects occur. Long-term infusions should be initiated at 4 ng/kg/min less than the maximum tolerated infusion rate determined during short-term-dose-ranging. If the maximum tolerated infusion rate is less than 5 ng/kg/min, the long-term infusion should be started at one-half the maximum tolerated infusion rate.²³

The dose of epoprostenol varies greatly among and within patients over the course of treatment. The dose required to control symptoms generally must be increased over time as tolerance develops.²³ The dose of 20 - 40 ng/kg/min is suggested as the optimal dose for the majority of patients in the European Guidelines on pulmonary hypertension.¹⁹

Excluding VAT, epoprostenol costs £125.00 per 1.5 mg vial (MIMS March 09). Assuming daily use of two or three vials based on the European Society of Cardiology¹⁹ suggested optimal dose (20 - 40 ng/kg/min and bodyweight of 70 kg), results in an annual drug cost per patient of approximately £91,250 - £136,875. Other costs, including infusion pumps (two are needed by each patient in case of failure), lines etc are not included in these estimates.

Iloprost

Iloprost should only be initiated and monitored by a physician experienced in the treatment of PAH. Iloprost is intended for inhalation by nebulation. The recommended dose is 2.5 micrograms (as delivered at the mouthpiece) over four to five min, or 5.0 micrograms over eight to ten min.²⁷ The dose per inhalation session should be administered six to nine times daily according to individual need and tolerability. The patient must not use a face mask during inhalation. A dose of 2.5 micrograms should be used for the first inhalation, followed by 5.0 micrograms for the second inhalation. In case of poor tolerability of the 5.0 micrograms dose, the dose should be reduced to 2.5 micrograms. No dose adjustment is required in patients with a creatinine clearance > 30 ml/min.²⁷ Two compressed air nebuliser systems (HaloLite[®] and Prodose[®]), a portable battery-powered nebuliser (Venta-Neb[®]), and a portable vibrating mesh nebuliser (I-Neb[®] AAD[®]) have been shown to be suitable for the administration of Iloprost. Patients stabilised on one nebuliser should not switch to another without supervision by the treating physician.

Excluding VAT, iloprost costs £424.50 for 30 x 10 microgram vials, and £2377.20 for 168 x 10 microgram vials (MIMS March 09), resulting in an annual drug cost of approximately £30,989 - £46,483 per patient. The cost for iloprost assumes the use of one vial per inhalation session. This does not include the cost of the nebulising systems.

ENDOTHELIN ANTAGONISTS

Bosentan

Bosentan should only be initiated and monitored by a physician experienced in the treatment of PAH. Bosentan is administered orally and the recommended dose is 62.5 mg twice daily for four weeks, increased to a maintenance dose of 125 mg twice

daily.³⁴ Some patients not responding to 125 mg twice daily may benefit from 250 mg twice daily. However a careful risk/benefit assessment should be made, taking into consideration that liver toxicity is dose-dependent.³⁴ No dose adjustment is required in patients with renal impairment.³⁴

Liver aminotransferase levels must be measured prior to initiation of treatment and subsequently at monthly intervals for the duration of treatment with bosentan.³⁴ In addition, liver aminotransferase levels must be measured two weeks after any dose increase. It is recommended that haemoglobin concentrations be checked prior to initiation of treatment, every month during the first four months and quarterly thereafter.³⁴ Treatment should not be initiated in women of child-bearing potential unless they practice reliable contraception and the result of the pre-treatment pregnancy test is negative. If necessary, monthly pregnancy testing should be undertaken.³⁴

Excluding VAT, bosentan costs £1,4937.07 for 56 x 62.5 mg or 56 x 125 mg tablets (MIMS March 09), resulting in an annual drug cost of approximately £19,463 per patient at the maintenance dose (125 mg twice daily). This does not include the cost of monthly liver function monitoring, pregnancy testing and haemoglobin monitoring.

Sitaxentan

Sitaxentan is administered orally and the recommended dose is 100 mg once daily.⁴¹ Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH. In the case of clinical deterioration despite sitaxentan treatment for 12 weeks, alternative therapies should be considered. However, a number of patients who showed no response by week 12 of treatment responded favourably by week 24, so an additional 12 weeks of treatment may be considered. No dose adjustment is required in patients with renal impairment.⁴¹

Liver aminotransferases must be measured prior to initiation of treatment and subsequently at monthly intervals.⁴¹ It is recommended that haemoglobin concentrations be checked prior to treatment, after one and three months, and every three months thereafter.⁴¹ Treatment should not be initiated in women of child-bearing potential unless they practice reliable contraception. If necessary, monthly pregnancy testing should be undertaken.⁴¹

Excluding VAT, sitaxentan costs £1,540 for 28 x 100 mg tablets (MIMS March 09), resulting in an annual drug cost of approximately £20,075 per patient. This does not include the cost of monthly liver function monitoring, pregnancy testing and haemoglobin monitoring.

Ambrisentan

Ambrisentan is administered orally and the recommended dose is 5 mg once daily with or without food; increasing the dose to 10 mg once daily may be considered if the 5 mg dose is tolerated.⁵¹ Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH. There is limited experience with ambrisentan in individuals with severe renal impairment (creatinine clearance <30 ml/min); initiate therapy cautiously in this subgroup and take particular care if the

dose is increased to 10 mg.⁵¹

Liver aminotransferases must be measured prior to initiation of treatment and subsequently at monthly intervals.⁵¹ It is recommended that haemoglobin concentrations and/or the haematocrit be checked prior to treatment, after one month, and periodically thereafter.⁵¹ Treatment should not be initiated in women of child-bearing potential unless they practice reliable contraception and the result of the pre-treatment pregnancy test is negative. If necessary, monthly pregnancy testing should be undertaken.⁵¹

Excluding VAT, ambrisentan costs £1,651.07 for 30 x 5 mg or 30 x 10 mg tablets (MIMS March 09), resulting in an annual drug cost of approximately £20,088 per patient. This does not include the cost of monthly liver function monitoring, pregnancy testing and haemoglobin monitoring.

PHOSPHODIESTERASE INHIBITORS

Sildenafil

Sildenafil is administered orally and the recommended dose is 20 mg three times daily.⁵⁵ Tablets should be taken approximately 6 to 8 hours apart with or without food. Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH. Initial dosage adjustments are not required in patients with renal impairment, including severe renal impairment (creatinine clearance <30 ml/min). A downward dose adjustment to 20 mg twice daily should be considered after careful benefit-risk assessment only if therapy is not well-tolerated. Sildenafil has been shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors or nitrates in any form is therefore contraindicated.⁵⁵ Only the licensed product Revatio® should be used to treat patients with PAH, and not Viagra®, which is only licensed for the treatment of male erectile dysfunction.

Excluding VAT, sildenafil costs £373.50 for 90 x 20 mg tablets (MIMS March 09), resulting in an annual drug cost of approximately £4,544 per patient.

Table 1. Annual drug costs of treating a patient with PAH.

Drug	Regimen	Annual cost (52 weeks)
Epoprostenol (i.v.)	20 ng/kg/min - 40 ng/kg/min	£91,250 - £136,875*
Iloprost (nebulation)	2.5 – 5 micrograms, six to nine times daily	£30,989 - £46,483
Bosentan	125 mg twice daily	£19,463
Sitaxentan	100 mg once daily	£20,075
Ambrisentan	5 – 10 mg once daily	£20,088
Sildenafil	20 mg three times daily	£4,544

Doses are shown for general comparison and do not imply therapeutic equivalence.

* The dose for epoprostenol is difficult to determine; costs assume daily use of two or three vials based on the European Society of Cardiology suggested optimal dose of 20 – 40 ng/kg/min.¹⁹

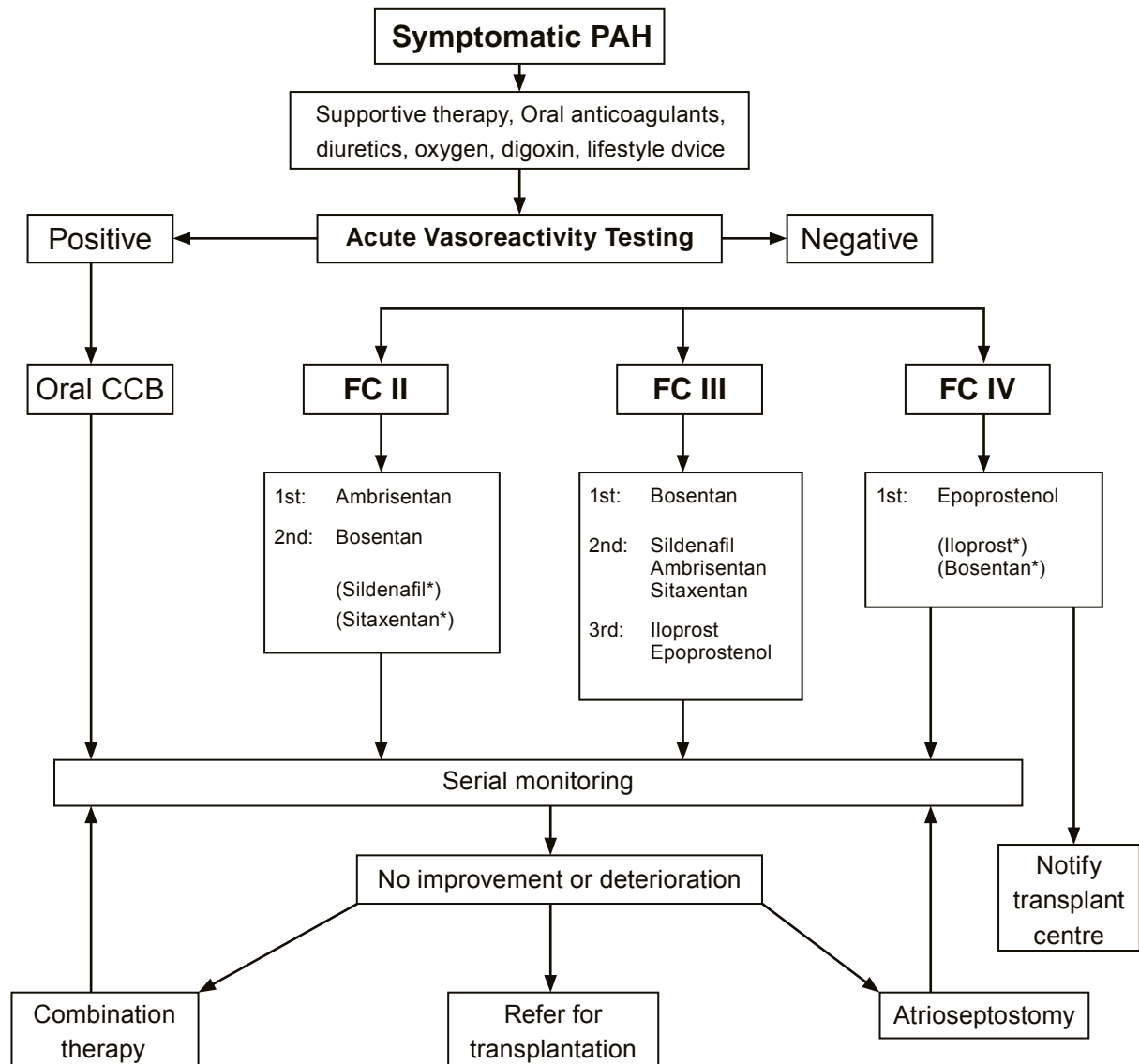
PLACE IN TREATMENT

There are a number of methodological weaknesses in many of the studies, including short-term follow-up periods, small sample sizes and diverse populations that vary greatly in aetiology, functional class, and prognosis. These limitations reflect in part the nature of the disease, in particular its low prevalence and the high mortality, which has limited the duration of many placebo-controlled trials to around 12 weeks due to ethical concerns.

Therapeutic strategies for treatment of PAH have been addressed in three major consensus documents, which propose similar evidence-based therapeutic algorithms.^{1,19,66} The choice of therapy is largely dependent on the severity of PAH at presentation. Newly diagnosed patients should undergo acute vasoreactivity testing and those demonstrating a positive response should be considered as candidates for oral CCBs. In all other patients, including those who do not show evidence of benefit after three months of CCB therapy, alternative disease-specific treatment based on functional class should be considered.^{1,19,66} It should be noted that functional class is difficult to determine, and may vary among patients and care providers. Furthermore, functional class may not always correlate with other indexes of disease severity, although in patients with IPAH it has been shown to correlate with outcome.¹ The factors that guide the choice of therapy include the side-effect profile of the therapy, method of administration, patient preference, cost effectiveness and clinical judgement.

The treatment algorithm presented in figure 1. summarises the current approach to therapy for PAH, based upon functional class.^{1,19,66} The algorithm is restricted to patients in NYHA/ WHO functional class II to IV as there is no evidence to support the treatment of patients in functional class I . Since the different treatments have largely been evaluated in patients with IPAH, caution should be used when extrapolating to patients with other forms of PAH.

Figure 1. Treatment Algorithm for PAH. Adapted from ^{1,19,66}



The prefixes 1st and 2nd indicate preferred and alternative drugs based on the quality and weight of clinical trial evidence, and expert opinion. CCB = calcium channel blocker; FC = functional class (WHO/NYHA); PAH = pulmonary arterial hypertension

* Unlicensed for this patient group

FUNCTIONAL CLASS II

First choice

Ambrisentan was the first targeted therapy approved in the UK for the treatment of patients with PAH in functional class II.⁵¹ In studies involving a limited number (38%) of functional class II patients ambrisentan statistically significantly improved exercise capacity and delayed clinical worsening compared to placebo.^{51,52}

Second choice

Bosentan has recently been licensed for the treatment of patients in functional class II.⁶⁷ In a study done exclusively in patients with mildly symptomatic PAH, bosentan was associated with statistically significant improvements in PVR. However, the drug had no statistically significant effect on exercise capacity.³⁷ In the SUPER study, in which approximately one-third of patients were in functional class II, sildenafil was associated with significant improvements in exercise capacity and haemodynamic outcomes, suggesting it may be of major benefit in this patient group.^{56,57} However, long-term data are largely derived from studies using four times the recommended daily dose and sildenafil is not currently licensed for use in this patient group.^{56,57} Sitaxentan has shown a similar degree of benefit to sildenafil in patients in functional class II but is also not currently licensed for this patient group.⁴²⁻⁴⁴ Evidence regarding the use of other targeted therapies in this patient group is limited.

FUNCTIONAL CLASS III

Non-responders to vasoreactivity testing, or those on high dose CCBs who demonstrate no improvement after one month of therapy or are unable to achieve functional class I or II after three months of therapy should be considered candidates for one of the four currently approved oral therapies (bosentan, sildenafil, sitaxentan or ambrisentan). Although no direct head-to-head comparisons have been made the clinical benefit in the short-term appears to be comparable for all oral therapies. Despite differences in enrolment criteria, patient populations, study duration and clinical outcomes evaluated, all oral therapies were associated with significant improvements in exercise capacity (6MWT). The results with respect to clinical worsening or change in functional capacity are more variable, with significant improvements being observed in some studies, but not in others.

First choice

Of the four currently available oral therapies, the quality and weight of evidence supports the use of bosentan as the first choice treatment in patients with PAH in functional class III.³⁵⁻³⁷ In PAH populations with mixed functional class (II, III and IV), and more specifically in functional class III, bosentan treatment resulted in statistically significant improvements in exercise capacity, haemodynamic outcomes, and PAH-associated dyspnoea compared to placebo. Bosentan treatment demonstrated not only symptomatic benefits, but also significantly decreased the rate of clinical worsening and improved long-term survival compared to predicted

rates. Liver abnormalities are a recognised class effect associated with ETRAs, and patients taking these agents require continuous monthly monitoring of liver function.^{34,41,51}

Second choice

Patients with liver abnormalities, or inability to have liver function monitored on a monthly basis should be considered for treatment with sildenafil. Sildenafil has demonstrated statistically significant improvements in exercise capacity, haemodynamic outcomes, and functional class compared to placebo in PAH populations with mixed functional class (I, II, III and IV).^{56,57} Improvements in some quality of life measures were also observed. Sildenafil requires no specific laboratory monitoring,⁵⁵ and has significant cost advantages over other agents used in the treatment of PAH. However, patients taking nitrate medications should not use sildenafil because it may cause hypotension.⁵⁵ Patients with ocular disease or recurrent epistaxis may be better candidates for other oral therapies. Sitaxentan has shown statistically significant reductions in the risk of clinical worsening, increased exercise capacity, and improved functional class and haemodynamic outcomes compared to placebo in PAH populations with mixed functional class (II, III and IV).⁴²⁻⁴⁸ However, the improvements observed in functional class specifically in those patients in functional class III did not reach statistical significance. As with bosentan, sitaxentan requires monthly monitoring of liver function. Ambrisentan appears to have a benefit to risk ratio similar to that of bosentan and sitaxentan, and also requires monthly monitoring of liver function, but unlike these agents it has no interactions with warfarin-type anticoagulants.⁵¹⁻⁵⁴ In PAH populations with mixed functional class (I, II, III and IV), ambrisentan treatment was associated with statistically significant improvements in exercise capacity.^{52,53} Furthermore, improvements in functional class, rate of clinical worsening and quality of life were observed, although statistical significance was variable.

Third choice

Patients with more advanced disease in functional class III may require treatment with a prostacyclin.^{1,19} Inhaled iloprost has been shown to significantly improve exercise capacity, haemodynamic variables and functional class compared to placebo.^{28,29} However, the relatively short duration of action is a major drawback of this treatment since six to nine daily inhalations may be required to maintain the desired clinical effect. Treatment with inhaled iloprost is not intended to replace oral therapy but should be considered only as an alternative therapy for patients who fail or cease to tolerate oral therapy. Intravenous iloprost is not licensed for the treatment of PAH in the UK, and evidence regarding its efficacy in this setting is lacking. If patients deteriorate on inhaled iloprost then i.v. epoprostenol may be warranted.^{1,19} Epoprostenol has a rapid and predictable onset of action and has demonstrated significant improvements in exercise capacity and haemodynamics compared to conventional therapy alone and increased survival compared to historical control subjects.²⁴⁻²⁶ Despite its proven efficacy, epoprostenol therapy is cumbersome. Its half-life of no more than six minutes necessitates continuous infusion through a central venous catheter, use of an external portable infusion pump, careful training of the patient in preparing the medication daily and comprehensive

follow-up by specialised medical staff. Over time the dose of epoprostenol needs to be increased to maintain its clinical effects.²³ Significant adverse events related to the delivery system such as infection may lead to prolonged inpatient stays, and abrupt interruption of infusion may lead to rebound worsening of haemodynamics that may even be fatal. Because of the complexity of administration, epoprostenol should generally be reserved for patients with advanced disease or those refractory to other therapies.

FUNCTIONAL CLASS IV

Continuous i.v. epoprostenol is currently the only approved therapy for patients with PAH in functional class IV,²³ and should be considered as the treatment of choice for these most critically ill patients because of the rapid onset of action and demonstrated survival benefit.^{1,19} Patients with severe PAH should not generally be considered candidates for oral or inhaled agents as first-line therapy, unless they refuse i.v. therapy or are not considered capable of managing the complex delivery system.¹ However, no long-term data exist regarding the use of other agents in patients with PAH in functional class IV.

COMBINATION THERAPY

Patients who deteriorate or have a suboptimal response to monotherapy may be candidates for combination therapy.¹⁹ Combining agents that target different pathways offers the possibility of enhanced efficacy and may allow individual agents to be used in lower doses to minimize toxicity. However, combination therapy may result in interactions between the agents, with unexpected increases in toxicity, or altered plasma concentrations (e.g. upon co-administration of bosentan and sildenafil, maximum plasma levels of sildenafil decreased by 55%, and bosentan levels increased by 42%⁶⁸). A favourable effect of combination therapy has been observed in several small, mostly open-label, or uncontrolled studies,^{33,59-63} but not in others.^{32,40} An appropriate protocol for suitable drug combinations is needed and further research is required to demonstrate the superiority of combination therapy over monotherapy.

SWITCHING THERAPIES

Switching from one agent to another may be considered for patients who fail to respond to initial treatment. However, there are currently no guidelines available for the selection of candidates for transitioning of therapies, the timing of, or the choice of agents.

FUTURE DEVELOPMENTS

The National Institute for Health and Clinical Excellence (NICE) is currently conducting a multiple technology appraisal reviewing the clinical and cost effectiveness of epoprostenol, iloprost, bosentan, sitaxentan, and sildenafil for the treatment of PAH in adults.⁶⁹ The timelines for this technology appraisal have been extended to allow the committee more time to consider a number of outstanding issues.⁷⁰ A date for publication of the final guidance has yet to be determined.

The European Society of Cardiology guidelines for the treatment of PAH are currently being reviewed and new guidelines are expected to be published in 2009.⁷¹

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REFERENCES

1. Badesch DB, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. *Chest* 2007;131:1917-28.
2. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med* 2004;351:1425-36.
3. Rubin LJ. Diagnosis and management of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;126:7S-10S.
4. Rosenkranz S. Pulmonary hypertension: current diagnosis and treatment. *Clin Res Cardiol* 2007;96:527-41.
5. Simonneau G, Galie N, Rubin LJ et al. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2004;43:5S-12S.
6. McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. *Circulation* 2006;114:1417-31.
7. Loyd JE. Genetics and pulmonary hypertension. *Chest* 2002;122:284S-86S.
8. Hoeper MM, Oudiz RJ, Peacock A et al. End points and clinical trial designs in pulmonary arterial hypertension: clinical and regulatory perspectives. *J Am Coll Cardiol* 2004;43:48S-55S.
9. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.
10. Barst RJ, McGoon M, Torbicki A et al. Diagnosis and differential assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2004;43:40S-47S.
11. Peacock AJ, Murphy NF, McMurray JJ, Caballero L, Stewart S. An epidemiological study of pulmonary arterial hypertension. *Eur Respir J* 2007;30:104-9.
12. Humbert M, Sitbon O, Chaouat A et al. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006;173:1023-30.
13. The Information Centre. Primary Diagnosis HES 2005-6, HES online. <http://www.hesonline.org.uk> Accessed 07/02/08
14. Rich S, Dantzker DR, Ayres SM et al. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987;107:216-23.
15. McGoon M, Gutterman D, Steen V et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;126:14S-34S.
16. Hamilton N, Elliot C. Pulmonary hypertension - the condition and specialist assessment. *Hospital Pharmacist* 2006;13:7-9.
17. Rubin LJ. Pulmonary arterial hypertension. *Proc Am Thorac Soc* 2006;3:111-5.
18. D'Alonzo GE, Barst RJ, Ayres SM et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991;115:343-9.
19. Galie N, Torbicki A, Barst R et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004;25:2243-78.
20. Puri A, McGoon MD, Kushwaha SS. Pulmonary arterial hypertension: current therapeutic strategies. *Nat Clin Pract Cardiovasc Med* 2007;4:319-29.
21. Hamilton N, Elliot C. Pulmonary hypertension - treatment options. *Hospital Pharmacist* 2006;13:10-14.

22. Lee SH, Rubin LJ. Current treatment strategies for pulmonary arterial hypertension. *J Intern Med* 2005;258:199-215.
23. GlaxoSmithKline UK. Summary of Product Characteristics. Flolan® Injection 0.5 mg and 1.5 mg. www.medicines.org.uk (last accessed 16/10/08).
24. Barst RJ, Rubin LJ, Long WA et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996;334:296-302.
25. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002;106:1477-82.
26. Sitbon O, Humbert M, Nunes H et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002;40:780-8.
27. Bayer Plc. Summary of Product Characteristics. Ventavis® 10mcg/ml nebuliser solution. www.medicines.org.uk (last accessed 16/10/08).
28. Olschewski H, Simonneau G, Galie N et al. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002;347:322-9.
29. European Medicines Agency. European Public Assessment Report – Venatvis - Scientific Discussion. <http://www.emea.europa.eu/humandocs/PDFs/EPAR/ventavis/106603en6.pdf> (last accessed 16/10/08).
30. Olschewski H, Nikkho S, Behr J et al. Long-term survival in patients with pulmonary hypertension inhaling iloprost. *Eur Heart J* 2003;24:482.
31. All Wales Medicines Strategy Group. Therapeutic development Assessment - Iloprost (Ventavis®). December 2006. [www.wales.nhs.uk/sites3/Documents/371/Enclosure 8 Iloprost report to AWMSG.pdf](http://www.wales.nhs.uk/sites3/Documents/371/Enclosure%208%20Iloprost%20report%20to%20AWMSG.pdf).
32. Hoeper MM, Leuchte H, Halank M et al. Combining inhaled iloprost with bosentan in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2006;28:691-4.
33. McLaughlin VV, Oudiz RJ, Frost A et al. Randomized Study of Adding Inhaled Iloprost to Existing Bosentan in Pulmonary Arterial Hypertension. *Am. J. Respir. Crit. Care Med.* 2006;174:1257-63.
34. Acetlition UK. Summary of Product Characteristics. Tracleer® 62.5 mg and 125 mg film-coated tablets. www.medicines.org.uk (last accessed 16/10/08).
35. Badesch D, Bodin F, Channick RN et al. Complete results of the first randomized, placebo-controlled study of bosentan, a dual endothelin receptor antagonist, in pulmonary arterial hypertension. *Current Therapeutic Research* 2002;63:227-46.
36. Rubin LJ, Badesch DB, Barst RJ et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346:896-903.
37. Galie N, Rubin L, Hoeper M et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008;371:2093-100.
38. Sitbon O, Badesch DB, Channick RN et al. Effects of the dual endothelin receptor antagonist bosentan in patients with pulmonary arterial hypertension: a 1-year follow-up study. *Chest* 2003;124:247-54.
39. McLaughlin VV, Sitbon O, Badesch DB et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. *Eur Respir J* 2005;25:244-9.
40. Humbert M, Barst RJ, Robbins IM et al. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J* 2004;24:353-59.
41. Encysive UK Ltd. Summary of Product Characteristics. Thelin® 100 mg film-coated tablets . <http://www.emea.europa.eu/humandocs/PDFs/EPAR/thelin/H-679-PI-en.pdf> (last accessed 16/10/08).

42. Barst RJ, Langleben D, Frost A et al. Sitaxsentan therapy for pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2004;169:441-7.
43. Barst RJ, Langleben D, Badesch D et al. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. *J Am Coll Cardiol* 2006;47:2049-56.
44. Pulido T, Kurzyna M, Souza R, Ramirez A, Sandoval J. Sitaxsentan 100 mg proves more effective than sitaxsentan 50 mg in patients with pulmonary arterial hypertension (PAH). *Proc Am Thorac Soc* 2006; 3; A417.
45. Frost AE, Langleben D, Oudiz R et al. The 6-min walk test (6MW) as an efficacy endpoint in pulmonary arterial hypertension clinical trials: demonstration of a ceiling effect. *Vascul Pharmacol* 2005;43:36-9.
46. Langleben D, Brock T, Dixon R, Barst R. STRIDE 1: Effects of the selective ET receptor antagonist, sitaxsentan sodium, in a patient population with pulmonary arterial hypertension that meets traditional inclusion criteria of previous pulmonary arterial hypertension trials. *J Cardiovasc Pharmacol* 2004;44:S80-S84.
47. Barst RJ. Sitaxsentan: a selective endothelin-A receptor antagonist, for the treatment of pulmonary arterial hypertension. *Expert Opin Pharmacother* 2007;8:95-109.
48. European Medicines Agency. European Public Assessment Report – Thelin - Scientific Discussion. <http://www.emea.europa.eu/humandocs/PDFs/EPAR/thelin/H-679-en6.pdf> (last accessed 16/10/08).
49. Horn EM, Widlitz AC, Barst RJ. Sitaxsentan, a selective endothelin-A receptor antagonist for the treatment of pulmonary arterial hypertension. *Expert Opin Investig Drugs* 2004;13:1483-92.
50. Horn E, Langleben D, Frost A et al. Long-term sitaxsentan therapy in Pulmonary Arterial Hypertension (PAH) P2831. *Eur Heart J* 2004;25:445-623
51. GlaxoSmithKline. Summary of Product Characteristics. Volibris® 5 mg and 10 mg film-coated tablets. www.medicines.org (last accessed 16/10/2008).
52. Galie N, Olschewski H, Oudiz RJ et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation* 2008;117:3010-9.
53. European Medicines Agency. European Public Assessment Report – Volibris - Scientific Discussion. <http://www.emea.europa.eu/humandocs/PDFs/EPAR/volibris/H-839-en6.pdf> (last accessed 16/10/08)
54. Oudiz R. Long-term ambrisentan therapy provides sustained benefit in patients with pulmonary arterial hypertension. *Chest* 2007;132:474a-.
55. Pfizer Ltd. Summary of Product Characteristics. Revatio® 20 mg film-coated tablets . www.medicines.org.uk (last accessed 16/10/08).
56. Galie N, Ghofrani HA, Torbicki A et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005;353:2148-57.
57. European Medicines Agency. European Public Assessment Report – Revatio - Scientific Discussion. <http://www.emea.europa.eu/humandocs/PDFs/EPAR/Revatio/30895705en6.pdf> (last accessed 16/10/08).
58. Wilkins MR, Paul GA, Strange JW et al. Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) study. *Am J Respir Crit Care Med* 2005;171:1292-7.
59. Hoepfer MM, Faulenbach C, Golpon H, Winkler J, Welte T, Niedermeyer J. Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2004;24:1007-10.

60. Simonneau G, Rubin MD, Galie N et al. Safety and efficacy of sildenafil-epoprostenol combination therapy in patients with pulmonary arterial hypertension (PAH). *Am J Respir Crit Care Med* 2007; 175:A300.
61. Simonneau G, Burgess G, Collings L et al. Safety and efficacy of combination therapy with sildenafil and epoprostenol in patients with pulmonary arterial hypertension (PAH). *Am J Respir Crit Care Med* 2006; A58.
62. Stiebellehner L, Petkov V, Vonbank K et al. Long-term treatment with oral sildenafil in addition to continuous IV epoprostenol in patients with pulmonary arterial hypertension. *Chest* 2003;123:1293-5.
63. Ghofrani HA, Rose F, Schermuly RT et al. Oral sildenafil as long-term adjunct therapy to inhaled iloprost in severe pulmonary arterial hypertension. *J Am Coll Cardiol* 2003;42:158-64.
64. Gilead Sciences. Full prescribing information. Letaris® 5 mg and 10 mg film-coated tablets. http://www.letairis.com/downloads/LETAIRIS_prescribing_information.pdf (last accessed 16/10/08).
65. National Commissioning Group (NCG) – Pulmonary Hypertension service for adults. http://www.ncg.nhs.uk/ncg_services.htm.
66. National Pulmonary Hypertension Centres of the UK and Ireland. Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland. *Heart* 2008;94 Suppl 1:i1-41.
67. European Medicines Agency. Committee for Medicinal Products for Human Use – Post Authorisation Summary of Positive Opinion for Tracleer 26/06/08 http://www.emea.europa.eu/pdfs/human/opinion/Tracleer_21027608en.pdf (last accessed 16/10/08).
68. Burgess G, Hoogkamer H, Collings L, Dingemans J. Mutual pharmacokinetic interactions between steady-state bosentan and sildenafil. *Eur J Clin Pharmacol* 2008;64:43-50.
69. The National Institute for Health and Clinical Excellence. Appraisals in development: Pulmonary arterial hypertension (adults) - Drugs for the treatment of pulmonary arterial hypertension. <http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11708> (Last updated 21/08/2008).
70. The National Institute for Health and Clinical Excellence. Pulmonary arterial hypertension (adults) - drugs: letter to consultees and commentators regarding delay to the appraisal. 21/08/2008. <http://www.nice.org.uk/guidance/index.jsp?action=download&o=41701>
71. The European Society of Cardiology. Guidelines Publication Schedule. Guidelines on Pulmonary Arterial Hypertension (New Version). <http://www.escardio.org/guidelines-surveys/esc-guidelines/Pages/publication-schedule.aspx> (accessed 13/03/2009).

APPENDICES

APPENDIX 1. REVISED CLINICAL CLASSIFICATION OF PULMONARY HYPERTENSION (Venice 2003).⁵

1. Pulmonary arterial hypertension

- 1.1. Idiopathic (PAH)
- 1.2. Familial (FPAH)
- 1.3. Associated with: (APAH)
 - 1.3.1. Collagen vascular disease
 - 1.3.2. Congenital left-to-right shunt
 - 1.3.3. Portal hypertension
 - 1.3.4. Infection with human immunodeficiency virus
 - 1.3.5. Drugs and toxins
 - 1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy)
- 1.4. Associated with substantial venous or capillary involvement
 - 1.4.1. Pulmonary veno-occlusive disease (PVOD)
 - 1.4.2. Pulmonary capillary haemangiomas (PCH)
- 1.5. Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension with left heart disease

- 2.1. Left-sided atrial or ventricular heart disease
- 2.2. Left-sided valvular heart disease

3. Pulmonary hypertension associated with lung disease or hypoxemia or both

- 3.1. Chronic obstructive pulmonary disease
- 3.2. Interstitial lung disease
- 3.3. Sleep-disordered breathing
- 3.4. Alveolar hypoventilation disorders
- 3.5. Chronic exposure to high altitude
- 3.6. Developmental abnormalities

4. Pulmonary hypertension due to chronic thrombotic or embolic disease or both

- 4.1. Thromboembolic obstruction of proximal pulmonary arteries
- 4.2. Thromboembolic obstruction of distal pulmonary arteries
- 4.3. Non-thrombotic pulmonary embolism (tumour, parasites, foreign material)

5. Miscellaneous:

Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumour, and fibrosing mediastinitis)

APPENDIX 2. NYHA/WHO CLASSIFICATION OF FUNCTIONAL STATUS OF PATIENTS WITH PAH.

	NYHA definition ⁹	WHO definition ^{6,10}
Class I	Patients with cardiac disease without concomitant limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea, or anginal pain.	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause dyspnoea or fatigue, chest pain or near syncope
Class II	Patients with cardiac disease that results in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea, or anginal pain.	Patients with pulmonary hypertension resulting in slight limitation of physical activity. These patients are comfortable at rest, but ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.
Class III	Patients with cardiac disease that results in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea, or anginal pain.	Patients with pulmonary hypertension resulting in marked limitation of physical activity. These patients are comfortable at rest, but less than ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.
Class IV	Patients with cardiac disease that results in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Patients with pulmonary hypertension resulting in inability to perform any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may be present at rest, and discomfort is increased by any physical activity.

APPENDIX 3. SUMMARY OF KEY TRIALS

Key: ALT – alanine aminotransferase; AST – aspartate aminotransferase; C – controlled; CCB – calcium channel blocker; CHD – congenital heart disease; CI – confidence interval; CS – case series; CTD – connective tissue disease; DB – double-blind; FC – functional classification; FEV₁ – forced expiratory volume; FVC – forced vital capacity; HC – historic control; HIV – human immunodeficiency virus; IPAH – idiopathic pulmonary arterial hypertension; ITT – intention-to-treat; i.v. – intravenous; MC – multicentre; mPAP – mean pulmonary artery pressure; NS – not significant; NYHA – New York Heart Association; OL – open label; Ole – open label extension; Pbo – placebo controlled, PC – prostacyclin; PCWP – pulmonary capillary wedge pressure; PDE-5 – phosphodiesterase-5; PH – pulmonary hypertension; PPH – primary pulmonary hypertension; PVR – pulmonary vascular resistance; QoL – quality of life; R – randomised; TPR – total pulmonary resistance; U – uncontrolled; ULN – upper limits of normal; VO₂ peak oxygen consumption – WHO – World Health Organisation; yrs – years; 6MWT – six-minute walk test.

Trials involving epoprostenol

Reference	Design	Intervention	Patient Numbers	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Barst et al, 1996. ²⁴	R, OL, MC	Epoprostenol started at 2 ng/kg/min increased to maximum tolerated dose.	81 (NYHA FC III 74%, IV 26%)	PPH in NYHA class III or IV despite optimal conventional therapy.	Not stated.	6MWT.	At week 12 the median change from baseline in the 6MWT was +31 m for epoprostenol group vs.. -29 m for conventional therapy alone (p<0.002). Epoprostenol significantly reduced mPAP (p<0.002) and PVR (p<0.001), and improved QoL indices (p<0.01) vs. conventional therapy alone.	Jaw pain, headache, diarrhoea, flushing and nausea/vomiting. 4 episodes of non-fatal catheter sepsis and 1 non-fatal thrombotic event. 26 episodes of drug-delivery system malfunctions.
McLaughlin et al, 2002. ²⁵	OL, HC	Epoprostenol started at 2 ng/kg/min increased to maximum tolerated dose.	162 (NYHA FC III 46%, IV 54%)	PPH in NYHA class III or IV treated with i.v. epoprostenol.	Not stated.	Survival rate.	Survival rates at 1, 2 and 3yrs were 87.8%, 76.3%, 62.8% compared with 58.9%, 46.3% and 35.4% based on historical data (p<0.001).	119 local infections, 70 episodes of sepsis, 10 tunnel infections. 4 patients died of sepsis and 1 patient died after interruption of epoprostenol infusion.
Sitbon et al, 2002. ²⁶	OL, HC	Epoprostenol started at 1 ng/kg/min increased to mean dose 14 ± 4 ng/kg/min at 3 months	178 (NYHA FC III 67%, IV 33%)	>15 yrs, PPH in NYHA class III or IV treated with long-term i.v. epoprostenol.	PH due to CTD, CHD, HIV, portal hypertension, or chronic pulmonary disease, distal chronic thromboembolic PH, positive acute pulmonary vasodilator response.	Survival rate.	Survival rates at 1, 2, 3 and 5yrs were 85%, 70%, 63% and 55% compared with 58%, 43%, 33% and 28% in historical controls (p<0.0001).	Jaw pain, headache, diarrhoea, flushing, leg pain and nausea/vomiting. 76 episodes catheter-related sepsis, in 53 patients, leading to death in 4 patients. Severe pulmonary oedema caused death in 7 patients.

Trials involving iloprost

Reference	Design	Intervention	Patient Numbers	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Olschewski et al, 2002. ²⁸ (AIR)	R, C, MC, Pbo	Inhaled iloprost 2.5 micrograms (9%) or 5.0 micrograms (91%), six or nine times daily (mean 7.5). Median dose 30 micrograms/ day.	101 (NYHA FC III 59%, IV 41%)	PPH, PH associated with appetite suppressants, scleroderma, and inoperable chronic thromboembolic PH. mPAP >30 mmHg, 6MWT of 50 - 500m, NYHA III or IV. Doses of CCBs stable for >6 weeks.	PCWP at rest >15 mmHg, cardiac index <1.5, or >4 L/min/m ² bleeding disorders, bilirubin >3mg/dl, creatinine clearance <30ml/min, FVC <50%, FEV ₁ <mean-2sd, clinical instability, treatment with investigational drugs, prostanoids or beta-blockers.	Combined endpoint of both increase of ≥ 10% in 6MWT, and improvement in NYHA class in absence of clinical deterioration or death.	16.8% of patients achieved combined endpoint in iloprost group compared with 4.9% in placebo group (p=0.007). Estimated odds of an effect in iloprost group were 3.97 (95%CI, 1.47 to 10.75).	No significant difference between groups for overall number of adverse effects. Adverse events were significantly more frequent in the iloprost group than with placebo were: syncope (5% vs. 0%), flushing (27% vs. 9%), and jaw pain (12% vs. 3%).
		Placebo.	102 (FC III 58%, IV 42%)					
Olschewski et al, 2003. ²⁹⁻³¹ (AIR-2)	R, C,OL, MC	Inhaled iloprost 100 micrograms (range 50-200 micrograms) six times daily (range 3-12), plus conventional therapy.	30 (NYHA FC II, 33%, III 48%, IV 19%, all pts)	Similar to above.	Similar to above.	As above.	At week 12, significantly more patients achieved the combined end point in the iloprost group (13%) compared with the control group (0%, p=0.046).	Similar to those reported above with >20% frequency of vasodilatation and cough in the iloprost group.
		Conventional therapy alone.	33					

Trials involving iloprost cont.

Reference	Design	Intervention	Patient Numbers	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Hoepfer et al, 2006. ³² (COMBI)	R, C,OL, MC	Inhaled iloprost and 5 micrograms six times daily and bosentan 125 mg twice daily.	19 (all NYHA FC III)	IPAH in FC class III, bosentan therapy >3 months, 6MWT of 150 –425 m, and aminotransferase level 2 x below ULN.	Any other form of PAH, severe lung disease, clinical instability (right-heart failure, 6MWT <150 m, or systolic blood pressure <85 mm Hg), concomitant sildenafil therapy, or prostanoids treatment within prior 3 months.	Change in 6MWT at 12 weeks.	The trial was terminated early after a futility analysis predicted failure with respect to predetermined sample size. Primary endpoint not met. Mean change in 6MWT +1 m and -9 m in control and combination groups, respectively.	One case of pneumonia reported in the combination group, and one case of upper respiratory tract infection in the control group. One patient stopped iloprost due to intractable coughing. Other adverse effects reported in the combination group were diarrhoea (n=2), headache and flushing (n=2), and haemoptysis (n=1), all mild in intensity.
		Bosentan 125 mg twice daily	21 (all FC III)					
McLaughlin et al, 2006. ³³ (STEP)	R, C, DB, MC	Inhaled Iloprost 5 micrograms per inhalation and bosentan 125 mg twice daily.	34 (NYHA FC III 97%, IV 3%)	PAH, bosentan therapy ≥4 months, 6MWT of 100 – 425 m, mean PAP >25 mmHg, PCWP <15 mmHg, PVR ≥240 dyn s/cm ⁵	Thromboembolic disease, untreated obstructive sleep apnoea, portal hypertension, chronic liver disease, renal insufficiency, left-sided or un-repaired CHD, lung disease, and those receiving PDE-5 inhibitors or other prostanoids.	Not stated. (6MWT, FC, aemodynamics and time to clinical worsening)	At week 12 the change from baseline in the 6MWT was +30 m for the iloprost group vs. +4 m for placebo (p=0.051). FC improved by one class in 34% of iloprost versus 6% of placebo patients (p=0.002). Iloprost delayed the time to clinical worsening (p=0.0219), improved post-inhalation mPAP (p<0.001) and PVR (p<0.007). Changes in haemodynamics did not reach significance when measured pre-inhalation.	The overall the incidences of adverse events were similar in the two groups. The most common adverse events with iloprost (and >10% more frequent than with placebo) included headache (54% vs. 22%), cough (40% vs. 19%), jaw pain (29% vs. 9%), flushing (26% vs. 9%) and pharyngolaryngeal pain (20% vs. 6%).
		Bosentan 125 mg twice daily and placebo.	33 (FC II 3%, III 91%, IV 6%)					

Trials involving bosentan

Reference	Design	Intervention	Patient Numbers	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Badesch et al, 2001. ³⁵	R, DB, Pbo, MC	Bosentan 62.5 mg twice daily for 4 weeks then 125 mg twice daily for 12 weeks plus conventional treatment.	21 (all WHO FC III)	PPH or PH due to scleroderma, NYHA FC II–IV Baseline 6MWT 150 m – 500 m, mPAP P25 mm Hg, PCWP <15 mmHg, PVR >240 dyn s/cm ⁵ .	NYHA IV due to unstable clinical status), started or stopped any conventional treatment within one month of screening, receiving chronic treatment with epoprostenol received glibenclamide or ciclosporin within one month of enrolment.	6MWT at 12 weeks.	At week 12 the change from baseline in the 6MWT was +70 m for bosentan group vs. -6 m for placebo (difference 76 m [95% CI 12-139m], p=0.021). The improvement in 6MWT was maintained for at least 20 weeks.	Overall the incidence and nature of adverse events was similar between the two treatment groups (42.9% vs. 63.6% for bosentan and placebo, respectively). Increases in hepatic aminotransferases occurred in 2 bosentan patients (asymptomatic and returned to normal without discontinuation or dose change).
		Placebo plus conventional treatment.	11 (all FC III)					
Rubin et al, 2002. ³⁶ (BREATHE-1)	R, DB, MC, Pbo	Bosentan 62.5 mg twice daily for 4 weeks then 125 mg twice daily for 12 weeks plus conventional treatment.	74 (WHO FC III 92%, FC IV 8%)	PH (primary or associated with CTD). WHO III (n=195) or IV (n=18). Stable clinical status for class IV participants. Baseline 6MWT 150 m – 500 m, mPAP P25 mm Hg, PCWP <15 mmHg, PVR >240 dyn s/cm ⁵ .	Started or stopped any therapy for PAH within 1 month of screening, or if had received or had been scheduled to receive long-term treatment with epoprostenol within 3 months of screening, and glibenclamide or ciclosporin treatment.	6MWT at 16 weeks.	At week 16 the change from baseline in the 6MWT was +36 m for bosentan group vs. -8 m for placebo (difference 44 m [95% CI, 21 to 67 m], p<0.001). The improvement was more pronounced for 250 mg twice daily dose than for 125 mg twice daily dose. (+54 m; p<0.001 and +35 m p<0.01, respectively), although there was no significant difference between the two bosentan groups.	The overall the incidences of adverse events were similar in the two groups. The most common adverse events with bosentan (and more frequent than with placebo) were headache (21% vs. 19%), syncope (9% vs. 6%) flushing (9% vs. 4%) and abnormal hepatic function (9% vs. 3%). Increases in hepatic aminotransferase levels to >8 x ULN did not occur in the placebo group, but occurred in 2 patients in the 125 mg bosentan group and 5 patients in the 250 mg group (7%, p<0.1).
		Bosentan 62.5 mg twice daily for 4 weeks then 250 mg twice daily for 12 weeks plus conventional treatment.	70 (FC III 89%, FC IV 11%)					
		Placebo plus conventional therapy.	69 (FC III 94%, FC IV 6%)					

Trials involving bosentan cont.

Reference	Design	Intervention	Patient Numbers	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Galie et al, 2008. ³⁷ (EARLY)	R, DB, MC, Pbo.	Bosentan 62.5 mg twice daily for 4 weeks then 125 mg twice daily for 6 months weeks (62.5 mg if body weight <40 kg) plus conventional treatment.	93 (all WHO FC II)	IPAH, FPAH, or PAH associated with HIV infection, anorexigen use, CHD, CTD or auto-immune disease. Sildenafil use was allowed.	Use of prostacyclin or ERTA therapy.	Change from baseline in PVR and 6MWT at 6 months.	At month 6, PVR was 83.2% of baseline value in the bosentan group and 107.5% of baseline in the placebo group (treatment effect -22.6% p<0.0001). 6MWT did not improve significantly compared with placebo, (+19m, p=0.08).	The overall the incidences of adverse events were similar in the two groups. The most frequently reported adverse events in the bosentan group were nasopharyngitis and abnormal liver function test. The incidence of AST or ALT >3x ULN was 13% for bosentan vs. 2% for placebo
		Placebo plus conventional therapy.	92 (all FC II)					
Humbert et al, 2004. ⁴⁰ (BREATHE-2)	R, DB, MC, Pbo.	Epoprostenol (2 ng/kg/min increased at two-weekly intervals) and bosentan (62.5 mg twice daily for 4 weeks then 125 mg twice daily).	22 (NYHA FC III 77%, 23% FC IV)	PAH (primary or associated with CTD) in NYHA class III or IV, scheduled for epoprostenol therapy within 2 weeks of screening.	Moderate or severe interstitial lung disease, or had started or stopped any PAH treatment within one month of screening or were receiving glibenclamide, ciclosporin and/or tacrolimus.	Change from baseline in TPR at week 16.	At week 16, TPR decreased in both groups, with no significant difference between the groups (p=0.08).	The number of serious adverse events was similar in the two treatment groups. The most frequently reported adverse events were jaw pain, diarrhoea, flushing and headache. The only adverse event that occurred more frequently in the combination group, than placebo was leg oedema (27% vs. 9%). Asymptomatic abnormal hepatic function was more frequent in the placebo group than the combination group (18% vs. 9%, respectively).
		Epoprostenol and placebo.	11 (73% FC III, 27% FC IV)					

Trials involving sitaxentan

Reference	Design	Intervention	Patient Numbers	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Barst et al, 2004. ⁴² (STRIDE-1)	R, DB, Pbo	Sitaxentan 100 mg daily.	55 (NYHA FC II 29%, III 71%)	PAH (primary or associated with CTD or CHD), 16 – 75 years of age, and NHYA FC II, III or IV.	Significant parenchymal lung disease, portal hypertension, chronic liver disease, history of HIV, AST or ALT >3 x ULN, chronic renal insufficiency, use of prostacyclin or ETRA therapy within 30 days of study entry.	Change in % predicted peak VO ₂ at week 12.	Sitaxentan (300 mg) significantly improved % predicted peak VO ₂ compared with placebo (+3.1%, p<0.01). Sitaxentan 100 mg & 300 mg improved 6MWT (+35 m & +33 m respectively, p<0.01) compared with placebo.	The overall the incidences of adverse events were similar in the two groups. The most common adverse events with sitaxentan (and more frequent than with placebo) were headache (45% vs. 34%), peripheral oedema (21% vs. 17%), nausea (20% vs. 19%), nasal congestion (18% vs. 10%), and dizziness (12% vs.10%). The incidence of AST or ALT >3 x ULN was 3% for placebo, 0% sitaxentan 100 mg, 10% sitaxentan 300 mg, respectively.
		Sitaxentan 300 mg daily.	63 (FC II 33%, III 67%)					
		Placebo daily.	60 (FC II 33%, III 67%, IV 3%)					
Barst et al, 2006. ⁴³ (STRIDE-2)	R, DB, Pbo,	Sitaxentan 50 mg daily	62 (WHO FC II 34%, III 61%, IV 5%)	PAH (primary or associated with CTD or CHD), 12 – 75 years of age, and WHO FC II, III or IV.	Significant parenchymal lung disease, portal hypertension, chronic liver disease, history of HIV, AST or ALT >1.5 x ULN, chronic renal insufficiency, use of prostacyclin, PDE-5 inhibitor, ETRA, or any new type of PAH therapy within 30 days of study entry.	Change from baseline in 6MWT at week 18.	At week 18 the change from baseline in the 6MWT was +31.4 m (p=0.03) for sitaxentan 100 mg group, +24.2 m (p=0.07) for 50 mg group, and +29.5 m (p=0.05) for the bosentan group compared to -6.5 m for the placebo group.	The overall the incidences of adverse events were similar in the two groups. The most common adverse events with sitaxentan (and more frequent than with placebo) were oedema, nasal congestion, fatigue and insomnia. The incidence of AST or ALT >3 x ULN was 6% for placebo, 5% sitaxentan 50 mg, 3% sitaxentan 100 mg, and 11% for bosentan, respectively.
		Sitaxentan 100 mg daily	61 (FC II 42%, III 56%, IV 2%)					
		Placebo daily.	62 (FC II 37%, III 57%, IV 6%)					
		OL Bosentan 62.5 mg twice daily for 4 wks, then 125 mg twice daily	60 (FC II 37%, III 62%, IV 2%)					

Trials involving sitaxentan cont.

Reference	Design	Intervention	Patient Numbers	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Pulido et al, 2006. ^{44,48} (STRIDE-4)	R, DB, Pbo	Sitaxentan 50 mg daily.	34 (WHO FC II 61%, III 38%, IV 1%, all pts)	PAH (primary or associated with CTD or CHD), 12 – 75 years of age, and WHO FC II, III or IV.	Significant parenchymal lung disease, portal hypertension, chronic liver disease, and patients receiving non conventional PAH treatments (e.g. bosentan, iloprost and sildenafil).	Change from baseline in 6MWT at week 18.	At week 18 the change from baseline in the 6MWT was +58 m for sitaxentan 100 mg group vs. +22 m for 50 mg group (p=0.014). The study was underpowered to detect a between group difference versus placebo.	The incidence of AST or ALT >3x ULN was the same in each group (1 patient).
		Sitaxentan 100 mg daily.	32					
		Placebo daily.	32					

Trials involving ambrisentan

Reference	Design	Intervention	Patient Numbers	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Galie et al, 2008. ⁵² (ARIES -1)	R, DB, Pbo, MC	Ambrisentan 5 mg daily.	67 (WHO FC II 30%, III 60%)	Subjects with PAH associated with CTD, anorexigen use or HIV infection, WHO FC I-IV.	Current use of non-conventional PAH therapies (prostacyclin, ETRA and PDE-5 inhibitors).	Change from baseline in 6MWT at week 12.	At week 12 the mean placebo-adjusted change from baseline in the 6MWT was +51.4 m for ambrisentan 10 mg (p=0.0001) and +30.6 m for the 5 mg group (p=0.008).	The most common adverse events with ambrisentan and more frequent than with placebo in ARIES-1 and -2 included (placebo-adjusted frequency): peripheral oedema (6%), nasal congestion (4%), sinusitis (3%), flushing (3%) and palpitations (3%). ⁶⁴ ALT & AST elevations >3 x ULN reported in 0.8% of patients.
		Ambrisentan 10 mg daily.	68 (FC II 33%, III 54%)					
		Placebo daily.	Placebo daily. 67 (FC II 34%, III 61%)					
Galie et al, 2008. ⁵² (ARIES -2)	R, DB, Pbo, MC	Ambrisentan 2.5 mg daily.	64 (FC II 53%, III 45%)	As above.	As above.	As above.	At week 12 the placebo-adjusted change from baseline in the 6MWT was +59.4m for ambrisentan 5 mg (p=0.001) and +32.3m for the 2.5 mg group (p=0.022).	
		Ambrisentan 5 mg daily.	63 (FC II 44%, III 52%)					
		Placebo daily.	65 (FC II 37%, III 57%)					
Galie et al, 2008. ^{52,54} (ARIES-E)	O	Ambrisentan 2.5 mg, 5 mg or 10 mg daily, including patients previously randomised to placebo	383 (FC III 46%, IIIIV 54%)	Patients receiving at least one dose of ambrisentan in ARIES-1 and -2	As above	As above	In 280 patients (94%) completing 48 weeks of ambrisentan monotherapy, the mean change from baseline in the 6MWT at 48 weeks was +39 m. (One-year survival was comparable for the 2.5, 5 and 10 mg ambrisentan groups (range 94.7% -96.8%).	Long-term incidence of ALT & AST elevations >3x ULN comparable to ARIES-1 and -2.

Trials involving sildenafil

Reference	Design	Intervention	Patient Numbers	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Galie et al, 2005. ^{56,57} (SUPER-1)	R, DB, Pbo, MC	Sildenafil 20 mg three times daily.	69 (WHO FC II 35%, III 58%, IV 7%)	Subjects with PAH (primary, associated with CTD, or surgical repair), WHO FC I-IV.	Current therapy with epoprostenol, bosentan, iloprost or trepostinil and L-arginine. 6MWT of <100 m or >450 m.	Change in 6MWT from baseline at week 12	At week 12 the placebo-adjusted change from baseline in the 6MWT +45 m, +46 m and +50 m for sildenafil 20 mg, 40 mg and 80 mg, respectively (all p<0.001).	The most common adverse events (≥3%) with sildenafil and more frequent than with placebo included: headache (46% vs. 39%), flushing (12% vs. 4%), back pain (12% vs. 11%), dyspepsia (11% vs. 7%) diarrhoea, and pain in the limb (both 10% vs. 6%).
		Sildenafil 40 mg three times daily.	67 (FC II 34%, III 66%)					
		Sildenafil 80 mg three times daily.	71 (FC II 39%, III 59%, IV 1%)					
		Placebo three times daily.	70 (FC I 1%, II 46%, III 49%, IV 4%)					
Galie et al, 2005. ^{56,57} (SUPER-2)	Ole	Sildenafil 80 mg three times daily.	259 (FC not reported)	As above.	As above.	Not stated.	Subjects previously assigned to placebo reached a dose of 80 mg three times daily at week 24 and showed a mean increase from baseline in 6MWT of +46 m, in those previously assigned sildenafil the mean increase in 6MWT at week 24 was approximately +50 m.	The incidence of adverse events (normalised to sildenafil exposure) were comparable to those observed in the SUPER-1 study.

Trials involving sildenafil cont.

Reference	Design	Intervention	Patient Numbers	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Wilkins et al, 2005. ⁵⁸ (SERAPH)	R, DB,C	Sildenafil 50 mg twice-daily for 4 weeks then 50 mg three times daily.	14 (WHO FC III)	Subjects with PAH (idiopathic or associated with CTD), baseline 6MWT 150 m – 450 m.	Liver enzymes >3 x ULN, previous bosentan or sildenafil treatment, and urgent need for prostanoids therapy on clinical grounds	Change in right ventricle mass from baseline.	At week 16 there were no significant differences between the two treatment groups for any endpoint when analysed by ITT.	One patient assigned to sildenafil died suddenly during week 14 of treatment. Two patients on bosentan had clinical evidence of fluid retention and one developed haemoptysis. No clinically significant changes in haematologic or routine biochemical measurements (including liver function) were observed.
		Bosentan 62.5 mg twice daily for 4 weeks then 125 mg twice daily.	12 (WHO FC III)					
Hoepfer et al, 2004. ⁵⁹	CS, U	Bosentan 62.5 mg three times daily for 4 weeks then 125 mg twice daily.	9 (FC III 89%, IV 11%)	IPAH, in whom bosentan therapy caused transient clinical improvement, followed by a decline in exercise intolerance.	Not stated.	Not stated. (6MWT and cardiopulmonary exercise testing reported)	Three months after the addition of sildenafil significant improvements in 6MWT (p=0.007), and peak oxygen uptake (p=0.006) were observed compared with presildenafil baseline values. FC improved in three patients and remained unchanged in six.	No deaths, drug-related serious adverse events, or liver enzyme abnormalities were observed. All patients reported minor headache and flushing when sildenafil was added to bosentan, which resolved without dose adjustment.
Simmoneau et al, 2007. ^{60,61} (PACES)	R, DB, Pbo, MC.	Epoprostenol (dose not stated) and sildenafil (20 mg three times daily, titrated to 40 mg or 80 mg three times daily).	267 (FC I 1%, II 29%, III 64%, IV 6%)	Subjects with PAH (PPH or associated with CTD), FC I-IV, stable on epoprostenol.	Not stated.	6MWT at week 16.	At week 16 there was a mean placebo-adjusted increase in 6MWT of +26m (p=0.001).	Adverse events were similar for both treatment groups. No patients died in the combination group vs. 7 deaths in the epoprostenol group.
		Epoprostenol and placebo.						

Trials involving sildenafil cont.

Reference	Design	Intervention	Patient Numbers	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Ghofrani et al, 2003. ⁶³	O, U	Long-term inhaled iloprost (average nine inhalations per day; dose not stated) plus sildenafil slowly increased over 3-4 days with final dose 25 mg three times daily (n=9) and 50 mg three times daily (n=5).	14 (FC III 36%, IV 64%)	Subjects with PAH, fulfilling at least two of the following criteria after long-term inhaled iloprost: subjective clinical worsening, deterioration in 6MWT >20%, signs of increased RH load, syncope.	Not stated.	Not stated. (6MWT, FC and haemodynamics reported)	6MWT increased by +90 m (p=0.002), +82 m (p=0.014), and +93 m (p=0.002) compared to pre-sildenafil values at 3, 6, and 9 - 12 months, respectively. PVR significantly decreased compared with pre-sildenafil values after 3 months (p=0.036).	Limited data presented. No serious sildenafil-related adverse events were reported. Two patients died of severe pneumonia during the period of combined therapy.