NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for the treatment of pulmonary arterial hypertension in adults

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members before the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. To allow sufficient time for the overview to be circulated to Appraisal Committee members before the meeting, it is prepared before the Institute receives consultees' comments on the assessment report. These comments are therefore not addressed in the overview.

A list of the sources of evidence used in the preparation of this document is given in appendix A.

1 Background

1.1 The condition

Pulmonary arterial hypertension (PAH) is a diverse group of diseases of similar pathophysiology and clinical presentation. They are characterised by a progressive increase in pulmonary vascular resistance, which leads to right ventricular heart failure and premature death. PAH is classified according to its clinical features (table 1). In addition, patients with PAH are classified according to their functional capacity (table 2).

PAH is one of five subtypes of pulmonary hypertension. Previously, pulmonary hypertension was classified into two categories: primary pulmonary hypertension and secondary pulmonary hypertension, depending on the absence or presence of identifiable causes or risk factors. However, a new clinical classification of pulmonary hypertension based on pathophysiological mechanism, clinical presentation and therapeutic options was proposed in 1998. This 'Evian classification' (sometimes referred to as the WHO 1998

classification) includes five major categories, one of which is PAH. The term primary pulmonary hypertension was retained within this category and included the subcategories 'sporadic PAH' and 'familial PAH'. It was agreed that the term secondary pulmonary hypertension should be abandoned. In 2003, the Evian classification was further modified. The term primary pulmonary hypertension was removed and the subcategory of sporadic PAH was replaced by 'idiopathic PAH' (IPAH). The details of Venice 2003 clinical classification are listed in table 1.

Table 1: Clinical classification of pulmonary hypertension – Venice 2003

1. Pulmonary arterial hypertension (PAH) 1.1. Idiopathic (IPAH) 1.2. Familial (FPAH) 1.3. Associated with (APAH): 1.3.1. Connective tissue disease (CTD) 1.3.2. Congenital systemic to pulmonary shunts 1.3.3. Portal hypertension 1.3.4. HIV infection 1.3.5. Drugs and toxins 1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy) 1.4. Associated with significant venous or capillary involvement 1.4.1. Pulmonary veno-occlusive disease (PVOD) 1.4.2. Pulmonary capillary haemangiomatosis (PCH) 1.5. Persistent pulmonary hypertension of the newborn (PPHN)
2. Pulmonary hypertension associated with left heart diseases 2.1. Left-sided atrial or ventricular heart disease 2.2. Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung respiratory diseases and/or hypoxia 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 and/or embolic disease 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, fibrosing mediastinitis)

Because the term primary pulmonary hypertension was widely used before the advent of the Venice 2003 classification, this term is retained in the assessment report and in this overview if it was used in the original

publications/reports of individual studies. Where this term is retained it is regarded as interchangeable with IPAH.

The prognosis for patients with PAH receiving conventional treatments (before the advance of targeted therapies) is considered to be poor. In the 1980s, median survival at the time of diagnosis for patients with IPAH (primary pulmonary hypertension) receiving supportive treatment was 2.8 years. Patient survival was estimated as 68% at 1 year, 48% at 3 years and 24% at 5 years. One of the key factors determining prognosis is functional class (FC) (table 2). Patients with FC I or FC II in the 1980s cohort had a median survival of 58.6 months, while those with FC III had a median survival of 31.5 months. An extremely low median survival of 6 months was observed in patients with FC IV. Today, median survival times from diagnosis may be longer due to greater awareness of PAH, the development of specialised PAH services and treatment algorithms, and the potential for earlier diagnosis.

Table 2: NYHA/WHO classification of functional status of patients with pulmonary hypertension

Class	Description
I	Patients with pulmonary hypertension in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnoea, fatigue, chest pain or pre-syncope.
II	Patients with pulmonary hypertension who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnoea, fatigue, chest pain or pre-syncope.
III	Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnoea, fatigue, chest pain or pre-syncope.
IV	Patients with pulmonary hypertension who are unable to perform any physical activity and who may have signs of right ventricular failure at rest. Dyspnoea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

A number of measures are used to monitor disease severity, progression and response to treatment in PAH. Many of these relate to exercise capacity, haemodynamics and/or cardiac performance. Some of the key measures are: the 6-minute walk test/distance (6MWT/D), dyspnoea scores, pulmonary artery pressure (PAP), right arterial pressure (RAP), pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance (PVR) and cardiac output/cardiac index.

PAH is a rare condition and, as with such conditions, a lack of systematic and often poor data collection prevents reliable predictions of morbidity, mortality and trend data. The estimated annual incidence of IPAH is 1–2 cases per million population, while the annual incidence of PAH associated with other aetiologies is 1–2 cases per million population. The likely prevalence of PAH has been estimated to be 15–50 patients per million population in the UK, with suggestions that the estimate may be towards the upper end of this range. Assuming an adult population in England and Wales of 43.3 million, this would give an approximate upper estimate of 2165 patients with PAH.

People with PAH may remain relatively asymptomatic until the underlying disease process is advanced. The key initial symptoms are breathlessness on exertion, with possible chest pain (angina) and fainting (syncope). Accurate diagnosis can be difficult as symptoms are non-specific and there is often a long delay between the onset of symptoms and reaching a definitive diagnosis. This delay can be several years, and patients may have severe disease (and possibly signs and symptoms of right ventricular heart failure) by the time appropriate treatment is started. Loss of exercise capacity and, latterly, the capacity for daily living can be devastating to patients' quality of life and may also lead to depression, leading to further deterioration in quality of remaining life. PAH, and IPAH in particular, can occur at a relatively young age, elevating the impact of the disease on patients and their carers.

1.2 Current management

A variety of treatments commonly referred to as conventional therapy or background therapy have been used in the management of PAH since before the advance of targeted therapies. These include anticoagulation therapy, diuretics, oxygen, digoxin, and calcium channel blockers. They are still used in clinical practice in addition to the technologies under assessment (see page 41–44 of the assessment report). Conventional therapy is therefore referred to as 'supportive treatment' throughout this overview.

2 The technologies

Table 3: Summary description of technologies

Non-proprietary name	Epoprostenol	Iloprost	Bosentan	Sitaxentan	Sildenafil
Proprietary name	Flolan	Ventavis	Tracleer	Thelin	Revatio
Manufacturer	GlaxoSmithKline	Schering Health Care	Actelion Pharmaceuticals	Encysive	Pfizer
Method of administration	Continuous intravenous infusion	Inhalation through a nebuliser	Oral	Oral	Oral
Pharmacological class	Prostaglandin I2 analogue	Prostaglandin I2 analogue	Endothelin receptor agonist	Endothelin receptor agonist	Phosphodiesterase inhibitor
Dose ('BNF' edition 54)	Initial infusion rate 1-2 ng/kg/min increased until maximum benefit on haemodynamic parameters is achieved and/or dose limiting effects occur	2.5–5 micrograms 6–9 times daily, adjusted according to response	Initially 62.5 mg twice daily, increased after 4 weeks to 125 mg twice daily; max. 250 mg twice daily	100 mg once daily	20 mg three times daily
Acquisition cost ('BNF' edition 54)	500-microgram vial £64.57; 1.5-mg vial £130.07	10 micrograms in 1-ml unit-dose vials 30 vials £424.50; 168 vials £2377.20	62.5 mg 56-tab pack £1541.00; 125 mg 56-tab pack £1541.00	100 mg 28-tab pack £1540.00	20 mg 90-tab pack £373.50

Epoprostenol

Epoprostenol (also known as prostacyclin) is a synthetic analogue of prostaglandin I2. It is indicated for the intravenous treatment of primary pulmonary hypertension for people in FC III and FC IV who do not respond adequately to conventional therapy. Epoprostenol is contraindicated in people with a known hypersensitivity to the drug, congestive heart failure from severe left ventricular dysfunction, or who develop pulmonary oedema during dose ranging (see the summary of product characteristics [SPC] for full details of contraindications and side effects).

People receive initial treatment as inpatients under specialist care to enable intensive training for them and/or their carers in administering the drug. Close monitoring and emergency back-up are also needed. A great deal of ability and commitment is required from the patient and/or their carer to prepare and administer the drug under sterile conditions and to maintain sterility of the permanent central venous catheter. Ongoing education and training are vital and these are delivered regularly by a specialist nurse.

Iloprost

Iloprost is a stable prostaglandin I2 analogue developed for intravenous, oral and inhaled administration. Only the formulation for inhalation is licensed for PAH and therefore the other formulations have not been considered. Inhaled iloprost is licensed for the treatment of primary pulmonary hypertension in people in FC III to improve exercise capacity and symptoms. Iloprost is contraindicated in people with a known hypersensitivity to the drug; conditions where activity on platelets might be undesirable (for example active peptic ulcers, intracranial bleeds or trauma); severe coronary disease events (for example severe artery disease, angina or recent myocardial infarction); recent cerebrovascular events (for example stroke); pulmonary hypertension due to veno-occlusive disease; valvular defects with clinically relevant myocardial function disorders unrelated to pulmonary hypertension; and during pregnancy or breastfeeding. Furthermore, iloprost is not recommended for people with unstable pulmonary hypertension who have advanced right ventricular heart failure (see the SPC for full details of contraindications and side effects).

Treatment is usually initiated under specialist care with the patient admitted to hospital for about 3 days for training, education and monitoring of self delivery. Patients can return home once stabilised and trained. Patients receive two nebulisers (one as back-up), and consumables are delivered regularly to their home. Nebulisers are replaced approximately every 2 years. Support from the specialist centre is readily available.

Bosentan

Bosentan is a dual endothelin receptor antagonist with affinity for both endothelin A and B (ETA and ETB). It is licensed to treat people with PAH in FC III to improve exercise capacity and symptoms. Two tablet sizes are available: 62.5 mg and 125 mg. Bosentan is contraindicated in people with a known hypersensitivity to the drug, hepatic impairment (including aminotransferases of more than three times the upper limit of normal) and those taking ciclosporin. Bosentan is contraindicated in pregnancy as it is assumed to be teratogenic, and women with child-bearing potential should not receive bosentan unless they are using a reliable contraceptive (bosentan may interact with and lessen the effectiveness of hormonal contraception) (see the SPC for full details of contraindications and side effects).

Patients are usually admitted to hospital as day cases under specialist care for the initiation of treatment. Patients return home and drugs are usually delivered to them at regular intervals.

Sitaxentan

Sitaxentan is a selective receptor antagonist for ETA (but not ETB). It is indicated in people with PAH in FC III to improve exercise capacity. Contraindications are similar to those of bosentan (above). There is significant interaction between sitaxentan and warfarin (see the SPC for full details of contraindications and side effects).

Patients are usually admitted to hospital as a day case under specialist care for the initiation of treatment. Some education is also given. Patients return home and drugs are usually delivered to them at regular intervals.

Sildenafil

Sildenafil is a specific inhibitor of phosphodiesterase-5. It is indicated to treat people with PAH in FC III to improve exercise capacity. It is contraindicated in people with a hypersensitivity to the drug, severe hepatic impairment, recent history of stroke or myocardial infarction, and severe hypotension at initiation. Use with nitric oxide-producing treatment or nitrates is not recommended as sildenafil potentiates the hypotensive effects of these agents. It is also

contraindicated in some specific eye conditions (see the SPC for full details of contraindications and side effects).

Patients are usually admitted to hospital as a day case under specialist care for the initiation of treatment. Some education is also given. Patients return home and drugs are usually delivered to them at regular intervals.

3 The evidence

3.1 Clinical effectiveness

3.1.1 Introduction

Randomised controlled trials (RCTs) were identified for each of the five technologies in this assessment. A summary of the distribution of RCTs across the technologies and the comparisons undertaken is available in appendix B of this overview. Most RCTs compared one technology plus supportive treatment with placebo and/or supportive treatment. There were few head-to-head comparisons of the technologies and few RCTs comparing a single technology with combination technologies. A summary of the characteristics of the trials identified by the Assessment Group is presented in appendix B. The Assessment Group presented results of meta-analyses (or individual trial results where only one trial provided data) for all the drugs in this appraisal.

3.1.2 Epoprostenol

The manufacturer of epoprostenol identified three open-label, parallel trials comparing epoprostenol added to supportive treatment with supportive treatment alone (Rubin 1990, Barst 1996, and Badesch 2000). A published study comparing epoprostenol with bosentan was identified by the manufacturer of bosentan, and a further, unpublished, study comparing epoprostenol with sildenafil was identified by the manufacturer of sildenafil. No further studies were identified by the Assessment Group. The three trials comparing epoprostenol with supportive treatment in patients with primary pulmonary hypertension are discussed here.

In all three trials, epoprostenol plus supportive treatment significantly improved exercise capacity (using the 6MWD measure) and haemodynamic measures compared with supportive treatment alone, and increased the proportion of patients with improved FC. Significant improvements in survival, PAH-associated symptom of dyspnoea and certain domains of quality of life measures were also observed in individual trials (see pages 86–89 of the assessment report).

Intention-to-treat analysis was reported only for survival and for 6MWD in Barst 1996 and only for 6MWD in Badesch 2000. The Assessment Group reported that the potential bias caused by this is most likely to be in favour of the control groups. Treatment withdrawal/loss to follow-up was not clearly reported in Rubin 1990 and Badesch 2000. The reporting of serious adverse events was also poor in all three trials. Data stratified by FC were not available. Results were summarised based on patient populations with mixed FC. All the epoprostenol trials were conducted in the USA, and consideration should be given to their generalisability to the UK patient population.

3.1.3 Iloprost

Two RCTs (AIR and AIR-2) compared inhaled iloprost added to supportive treatment with supportive treatment alone. The AIR-2 study remains unpublished at the time of writing. Two further RCTs (COMBI and STEP) identified by the Assessment Group compared iloprost added to ongoing bosentan therapy and supportive treatment with ongoing bosentan therapy and supportive treatment alone. The COMBI and STEP trials were not reported by the manufacturer as they considered combination therapy. The manufacturer identified and summarised further observational studies to support their clinical findings. The patient populations in these trials contained mixed subtypes of pulmonary hypertension and mixed FC.

In the AIR study iloprost plus supportive treatment significantly improved exercise capacity (6MWD) and haemodynamic measures compared with supportive treatment alone when measured post-inhalation. It also increased the proportion of patients with improved FC during 12 weeks of treatment.

Significant improvements in PAH-associated symptom of dyspnoea and EuroQol visual analogue scale were also observed. The manufacturer stated that there are data available on long-term survival with inhaled iloprost, although the published sample size is small; more extensive data will be published in due course. The Assessment Group considered that the number of deaths reported in AIR and AIR-2 was too small to draw any firm conclusions. The paucity of data prevents any inference being made specific to the licensed indication (primary pulmonary hypertension, FC III) (see pages 99–102 of the assessment report).

In the COMBI study of iloprost added to ongoing bosentan treatment plus supportive treatment, no significant difference was found between the iloprost group and the control group for any of the outcome measures. In contrast, the STEP study showed a significant reduction in the risk of clinical worsening and an increased likelihood of FC improvement for the iloprost group compared with the control group (patients treated with ongoing bosentan and supportive treatment). It also showed significant improvement in post-inhalation haemodynamic measures. The changes in 6MWD between treatment groups were not statistically significant in either of the trials (see pages 107–110 of the assessment report).

Both the AIR and the AIR-2 studies were carried out in mixed populations including IPAH and other subtypes of PAH within category 1 of the Venice classification, as well as other types of pulmonary hypertension (mainly chronic thrombolic, Venice category 4). The COMBI study recruited exclusively IPAH patients and the STEP study included mixed PAH populations (all within Venice category 1). The trials were also different in the mix of patients in terms of baseline FC: the AIR study included patients in FC III and IV, while the AIR-2 study also included patients in FC II. The COMBI study recruited only patients in FC III. The vast majority of patients in the STEP trial were in FC III at baseline. The AIR study was a multinational study conducted in Europe; the AIR-2 and COMBI trials were conducted in Germany; while the STEP study was conducted in the USA. Therefore,

consideration should be given as to whether the results are generalisable to the UK patient population.

3.1.4 Bosentan

Bosentan was investigated in six of the included RCTs. Four of these (Channick 2001, BREATHE-1, BREATHE-5 and STRIDE-2) compared bosentan with placebo (supportive treatment was allowed in the treatment and placebo arms of these studies). Another trial (BREATHE-2) compared the combination of epoprostenol plus bosentan with epoprostenol alone. Bosentan was compared with sitaxentan in STRIDE-2 and with sildenafil in a further study by Wilkins and colleagues (SERAPH). The manufacturer did not report on STRIDE-2 or SERAPH. The manufacturer reported data from a number of retrospective analyses and observational data to support their clinical findings.

Bosentan plus supportive treatment showed significant improvement in exercise capacity (6MWD) and haemodynamic outcomes compared with placebo plus supportive treatment, both in PAH populations with mixed FC and specifically in FC III. There was also a significant increase in time to clinical worsening, improvement in FC and PAH symptom of dyspnoea, and reduced risk of serious adverse events in bosentan treated patients compared with placebo in PAH populations with mixed FC. Subgroup analysis of PAH/connective tissue disease (CTD) patients in Channick 2001 and BREATHE-1 showed similar results to those of the whole trial population (see pages 122–125 of the assessment report). The manufacturer also used data from trials of lower quality to demonstrate that bosentan may be of benefit in patients with PAH associated with HIV, and that bosentan improves patients' quality of life.

Methods of randomisation and allocation concealment were not clearly described in some bosentan trials. Intention-to-treat analysis was used in most trials except in STRIDE-2. The Assessment Group stated that the potential bias from non-intention-to-treat analysis was expected to be small in STRIDE-2 as the number excluded from analysis in each treatment group was

very small. However, outcomes were not blindly assessed (such as clinical worsening, treatment withdrawal and adverse events) in this study, so interpretation requires greater caution, particularly in light of its open-label design.

BREATHE-2 compared the initiation of epoprostenol plus bosentan with epoprostenol alone in mixed PAH populations (IPAH and PAH/CTD) with mixed FC (III and IV). Methods of randomisation and allocation concealment were not clearly described in the published paper for this trial, and intention-to-treat analysis was not used for 6MWD. No significant difference was observed between the group treated with epoprostenol plus bosentan and the group treated with epoprostenol for any of the outcomes assessed in the trial (see pages 126–127 of the assessment report).

3.1.5 Sitaxentan

Sitaxentan was investigated in three of the included RCTs. All three trials (STRIDE-1, STRIDE-2 and STRIDE-4) compared sitaxentan with placebo in patients receiving ongoing supportive treatment. The STRIDE-2 trial also included an open-label bosentan arm; however, this section focuses on the comparison of sitaxentan added to supportive treatment with supportive treatment alone. The manufacturer identified three other observational long-term studies and a study evaluating the safety and efficacy of patients with PAH who had previously discontinued bosentan.

Sitaxentan at its licensed dose plus supportive treatment significantly reduced the risk of clinical worsening, increased exercise capacity (6MWD), and improved FC and haemodynamic outcomes compared with supportive treatment alone in PAH populations with mixed FC. Improvement in FC was observed in patients in FC III but this did not reach statistical significance. Post-hoc analysis suggested that the treatment effects of sitaxentan observed in the subgroup of PAH/CTD were similar to those observed in the whole trial populations. No significant differences were found between IPAH and PAH/CTD across various efficacy outcomes. Additional positive findings in physical health-related quality of life in the post-hoc analysis need to be

interpreted with caution and require further confirmation in future studies with prospectively planned analysis (see pages 136–139 of the assessment report).

Methods of randomisation and allocation concealment were adequate in all three trials. Intention-to-treat analysis was used in STRIDE-1 and STRIDE-4 but not in STRIDE-2. The Assessment Group stated that the extent of bias due to the exclusion of a small number of patients from efficacy analysis in STRIDE-2 was unclear. The STRIDE-1 study was conducted in North America; the STRIDE-2 study was an international study; and the STRIDE-4 trial was conducted mainly in South America but also Spain and Poland. Therefore consideration should be given to the generalisability of the results to the UK population.

3.1.6 Sildenafil

Sildenafil was investigated in six of the included RCTs. Four of these (SUPER-1, Bharani 2003, Sastry 2004 and Singh 2006) compared sildenafil with placebo in patients receiving ongoing supportive treatment (patients in Bharani 2003 appeared to have stopped previous vasodilator therapy before entering the study). Another trial (PACES-1), identified through the manufacturer's submission, compared sildenafil with placebo in patients receiving ongoing epoprostenol and supportive treatment. Sildenafil was compared with bosentan in a further study by Wilkins and colleagues (SERAPH). The manufacturer did not report results from Bharani 2003 or Singh 2006, and no rationale is provided for this omission. The manufacturer included two additional long-term extension studies and a further study comparing sildenafil with sildenafil plus iloprost (Ghofrani 2002). Ghofrani 2002 was excluded from the assessment report because its duration was less than 1 week (see page 248 of the assessment report).

Sildenafil at its licensed dose plus supportive treatment demonstrated significant improvement in exercise capacity (6MWD), haemodynamic outcomes, certain domains of quality of life measures and improvement in FC compared with supportive treatment alone in PAH populations with mixed FC.

Above-licence doses of up to 80 mg three times daily (the dose recommended in the SPC is 20 mg three times daily) appear to increase the treatment effect for these outcomes, although the differences between doses were not statistically significant in the trial. No significant improvement in time to clinical worsening or PAH symptom of dyspnoea were observed. The treatment effect of sildenafil in 6MWD was similar between primary pulmonary hypertension and PAH/CTD (see pages 148–150 of the assessment report). Results from PACES-1 indicated that patients treated with sildenafil at a dose of 80 mg three times daily had a significantly lower risk of clinical worsening and greater improvement in FC, 6MWD, some domains of quality of life measures and haemodynamic measures compared with placebo. There were no significant differences between sildenafil and placebo in changes in Borg Dyspnoea score, EQ-5D Utility Index and risk of serious adverse events (see pages 151–153 of the assessment report).

The manufacturer stated that the results from SUPER-1, supported by additional long-term data, demonstrate that sildenafil improves survival compared with supportive treatment alone. However, based on SUPER-1 data, the Assessment Group stated that the number of deaths observed is too small to draw any conclusions and that the difference between groups in the PACES-1 trial had just failed to reach statistical significance (see pages 148 and 151 of the assessment report).

Methods of randomisation and allocation concealment were considered to be adequate in SUPER-1. The primary analyses reported in this study excluded some patients with missing data and thus were not based on the intention-to-treat principle. However, intention-to-treat analyses were performed as sensitivity analyses and the results were consistent with its primary analyses. The fact that a large proportion of the study population was outside sildenafil's licensed indication in Bharani 2003, Sastry 2004 and Singh 2006, and their small sample sizes, should be taken into consideration when interpreting the results. Data from these studies were not meta-analysed by the Assessment Group.

3.1.7 Ongoing trials and long-term outcomes

The Assessment Group and the manufacturers identified a number of ongoing trials and long-term studies. The Assessment Group identified long-term studies to provide further information, in particular for the economic evaluation. The key requirement was for data to be provided according to FC for the outcomes: change (or no change) in FC and/or survival. Studies were included by the Assessment Group based on their duration and the number of patients enrolled (see appendices 6 and 7 of the assessment report for details of identified ongoing studies and long-term studies).

3.1.8 Summary of clinical effectiveness

The clinical effectiveness results show that significant improvements in FC, 6MWD and haemodynamic measures have been demonstrated in PAH populations for each of the technologies compared with placebo/control, although the volume of evidence varied among the technologies.

Many of the trials evaluated mixed populations of different PAH subcategories and/or FC; therefore, they do not directly relate to the licensed indication of individual technologies. None of the pivotal RCTs for the therapies under consideration had a study duration of more than 18 weeks. Some of the trials were conducted outside the UK population, which may affect the generalisability of the results to the population in England and Wales.

3.2 Cost effectiveness

3.2.1 Introduction

Four out of the five manufacturers and the Assessment Group provided estimates of cost effectiveness. As well as critically assessing the analyses carried out by the manufacturers, the Assessment Group developed its own Markov model to estimate the cost effectiveness of each of the five technologies versus supportive treatment. Due to the paucity of evidence, the Assessment Group model compared each technology with supportive treatment; no comparisons between the technologies were presented.

The Assessment Group identified four published economic evaluations in its literature search. These evaluations used three different approaches to modelling and none of the models produced results that were generalisable to the NHS.

The disparity in methods used among the manufacturers' submissions highlights that there is as yet no consensus as to the most appropriate model to use for the current technology assessment. This partly reflects the fact that the technologies are aimed at somewhat different groups of patients. There is some variability in the modelling approach, but more importantly in the type of economic evaluation used, with cost per quality-adjusted life year (QALY) and cost per life year being offered as efficiency measures. One submission also included a cost-minimisation analysis.

There is also wide variation in the methods, and the sources of data, used for calculating important model inputs such as survival estimates, quality of life (utility) scores and cost estimates.

Finally, a key issue is that of whether an appropriate comparator has been used. The various manufacturers' submissions are, in effect, not all addressing the same policy question.

3.2.2 Manufacturers' submissions

A summary of the manufacturers' economic evaluations is available in table 4 (page20).

Epoprostenol

The manufacturer of epoprostenol did not submit an economic evaluation.

Iloprost

The main issue with this economic evaluation is the choice of comparator. Iloprost was compared with epoprostenol and no comparison was made with supportive treatment. The manufacturer stated that epoprostenol is an appropriate comparator because it is consistent with UK clinical practice. The

Assessment Group found this claim was unsubstantiated and not consistent with the position adopted by the other manufacturers.

When compared with epoprostenol in the base-case analysis, iloprost was shown to reduce costs by £348,000 per person and increase QALYs by 0.04 per person. Therefore, according to the manufacturer's analysis, iloprost was dominant (more effective and less costly) over epoprostenol alone.

One-way sensitivity analysis showed results to be most sensitive to assumptions made about the proportion of patients improving with supportive treatment. Results were also sensitive to the cost of the drugs, but were less sensitive when the costs of managing PAH were included. Probabilistic sensitivity analysis demonstrated that at a threshold of £30,000 per QALY gained, the probability of iloprost being cost effective was 100% (see pages 184–188 of the assessment report).

Bosentan

Bosentan was compared with three comparators in the manufacturer's submission. These were historical care (defined as 30% of patients receiving the lowest-cost intravenous prostaglandins and 70% receiving supportive treatment), supportive treatment, and intravenous prostaglandins. The definition of historical care was based on audit data obtained from specialised PAH centres before the launch of bosentan. The submission states that supportive treatment alone is no longer a reasonable option. The manufacturer states that iloprost is historically the intravenous prostaglandin of choice, but because epoprostenol is cheaper, the latter is used in the model. In addition, epoprostenol efficacy is also used for intravenous prostaglandins due to intravenous iloprost data being limited. Two types of PAH were considered separately by the model: IPAH and PAH/CTD.

When compared with historical care in the base-case analysis for IPAH, bosentan was shown to increase costs by £20,000 per person and increase QALYs by 0.96 per person. Therefore the incremental cost-effectiveness ratio (ICER) for bosentan versus historical care was £21,000 per QALY gained. This rose to £84,000 per QALY gained when bosentan was compared with

supportive treatment. Bosentan dominated (was more effective and less costly) when compared to intravenous prostaglandins. When considered in the CTD group, bosentan was more cost effective. The ICER for bosentan versus historical care was £15,000 per QALY gained, rising to £78,000 per QALY gained when bosentan was compared with supportive treatment. Bosentan dominated (was more effective and less costly) when compared with intravenous prostaglandins.

The sensitivity analysis showed that the choice of comparator was central to the cost-effectiveness result. The modelling approach of counting costs and benefits only until the point of clinical worsening would have understated the cost and QALY estimates but it is not clear whether serious bias was introduced as a result of this. Results of the probabilistic sensitivity analysis (PSA) for IPAH patients showed bosentan to have a 40% probability of being cost effective compared with historic care at £20,000 per QALY, and 90% at £30,000, but not being cost-effective at either threshold when compared with supportive treatment. Analysis for CTD patients versus historical care gave 90% and 100% probabilities of bosentan being cost effective for £20,000 and £30,000 per QALY thresholds respectively, but not cost-effective when the comparator was supportive treatment (see pages 188–190 of the assessment report).

Sitaxentan

In the manufacturer's submission sitaxentan was compared with supportive treatment and bosentan. Benefits were expressed in life years gained rather than utilities.

Base-case results showed sitaxentan to be more effective (with a gain of 3.32 life years) than supportive treatment (2.70 life years) or bosentan (2.45 life years) but also more expensive. The ICER for sitaxentan compared with supportive treatment was £94,631 per life year gained, and £19,531 per life year gained when compared with bosentan.

Sensitivity analysis again shows that the choice of comparator is a key issue regarding cost effectiveness. Results of the PSA showed considerable

uncertainty, particularly in relation to supportive treatment where sitaxentan only had a 44% chance of being cost-effective at £80,000 per life year gained (see pages 191–192 of the assessment report).

Sildenafil

The manufacturer undertook a cost–utility analysis of sildenafil compared with background therapy (background therapy is not adequately defined in the manufacturer's submission). A cost-minimisation analysis was also undertaken comparing all five interventions. The manufacturer stated that this was because of the absence of evidence that there were any clinically meaningful efficacy differences between the five interventions.

Results of the base-case analyses gave an ICER of £22,058 per QALY gained for sildenafil versus background therapy. The PSA, run for 1000 iterations, suggested that sildenafil had an 84% probability of being cost effective at £30,000 per QALY gained, and 66% at £20,000.

In the cost-minimisation analysis, QALYs were assumed to be equivalent across intervention therapies as efficacy was assumed to be the same. Total costs and an average cost per QALY were presented for each therapy, with the lowest costs demonstrated by sildenafil.

The sensitivity analysis considered results over a 1-year period, and the ICER for sildenafil compared with background therapy was lower than in the base-case (life-time) at £15,252 per QALY gained. Total costs and average cost per QALY when compared with other intervention therapies also demonstrated that sildenafil had the lowest costs (see pages 192–194 of the assessment report).

Table 4: Summary of methods used in the manufacturers' submissions

Submission feature	Iloprost	Bosentan	Sitaxentan	Sildenafil
Therapy	Inhaled iloprost with switch to intravenous epoprostenol on reaching FC IV	Bosentan as first-line treatment	Sitaxentan as first-line treatment	Sildenafil as first-line treatment followed by iloprost or epoprostenol on failure
Comparator(s)	Intravenous epoprostenol	Historical care (30% iv prostaglandins, 70% supportive treatment); Supportive treatment alone; iv prostaglandins	Bosentan and supportive treatment	Background therapy, and each of the other four intervention therapies
Patient characteristics	Patients with primary pulmonary hypertension, FC III, who are unable to tolerate oral therapy. Age on initiation: 52	FC III, age sampled from distribution. Separate analyses for IPAH patients and those with connective tissue disease (CTD).	FC III, age 18+ (STRIDE trial populations)	FC III. Age 18+ with primary or secondary PAH from SUPER-1 and SUPER-2 studies. Age on initiation: 49
Form of analysis	Cost–utility analysis	Cost–utility analysis	Cost-effectiveness analysis (life years gained)	Cost–utility analysis (versus background therapy)
Model used	Markov model (with cohort of 100 patients and cycle length of 3 months)	Discrete event simulation (run for 10,000 hypothetical patients)	Markov model (with cycle length of 1 week)	Markov model of two distinct parts: year 1, year 2 onwards (with cycle length of 12 weeks (x3) and 16 weeks (x1) for year 1 and yearly cycle for year 2 onwards)
Time horizon of model	20 years	Length of time on bosentan before clinical worsening (death, change in treatment or need for transplantation)	5 years	30 years
Base-case results	Iloprost dominates epoprostenol alone (cost difference: £348,000, QALY difference: 0.04 per person)	IPAH: vs. historical care, £21,000 per QALY vs. epoprostenol, bosentan dominates vs. supportive therapy, £84,000 per QALY CTD: vs. historical care, £15,000 per QALY vs. epoprostenol, bosentan dominates vs. supportive therapy, £78,000 per QALY	vs. Bosentan, £19,531 per life year gained vs. supportive treatment, £94,631 per life year gained	Sildenafil vs. background therapy, £22,058 per QALY Cost-minimisation analysis: lowest cost for sildenafil

3.2.3 Assessment Group

The Assessment Group took into consideration the fact that the technologies are aimed at somewhat different groups of patients, which meant that a cost-effectiveness analysis comparing the technologies with one another was not possible. Therefore the Assessment Group's model compares each technology individually with supportive treatment. The results must be interpreted this way and not compared with each other. A summary of the Assessment Group model is available in table 5 (page 22).

The Assessment Group developed a Markov model, built in TreeAge, to determine the cost effectiveness of each technology plus supportive treatment compared with supportive treatment alone for PAH. The population considered was adults with PAH (category 1 of the Venice 2003 clinical classification 1 in FC III, and FC IV for epoprostenol) for whom calcium channel blockers were inappropriate or no longer effective. One reference case analysis was conducted, using data on all category 1 PAH patients. A separate analysis for IPAH alone was proposed but a lack of data prevented this.

All five technologies were considered. Only the first use of each intervention was considered, and initiation of any of the interventions after failure of another listed intervention was not considered, with the exception of epoprostenol for patients in FC IV. Therefore, for all treatments, the starting state was FC III with a further analysis conducted with a starting state of FC IV for epoprostenol. The analyses for iloprost, bosentan, sitaxentan and sildenafil were based on the assumption that all patients switch to intravenous epoprostenol upon deterioration to FC IV. Therefore, the supportive care arm in these analyses includes epoprostenol when FC IV is reached.

The resource use was broadly concerned with the initiation and ongoing costs of each intervention, contacts with primary and secondary health care, adverse events, and use of wider social services including palliative care. The perspective adopted for the reference case is that of the National Health Service and Personal Social Services, and a price year of 2006 was applied.

Additional model runs were undertaken to consider the three main issues. Firstly, there was an investigation of the effect on results when running the model for shorter time horizons of 10 and 20 years. Alternative therapy costs supplied by the manufacturers for inhaled iloprost and intravenous epoprostenol were incorporated. Finally, as there was more than one set of utility values to apply to the health states, those values not used in the reference case were explored.

Table 5: Summary of the features of the Assessment Group model

Model feature	Summary
Therapy	Epoprostenol, iloprost, bosentan, sitaxentan and sildenafil
Comparator(s)	Supportive treatment
Patient characteristics	Adults with pulmonary arterial hypertension (category 1 of the Venice 2003 clinical classification1 in FC III, and FC IV for epoprostenol) for whom calcium channel blockers were inappropriate or no longer effective.
Form of analysis	Cost–utility analysis
Model used	Markov model with 12-week cycle length
Time horizon of model	Lifetime (30 years)

Results

Independent economic evaluation suggests that bosentan, sitaxentan and sildenafil may be cost effective by standard thresholds and that iloprost and epoprostenol may not be cost effective.

The reference case for epoprostenol plus supportive treatment compared with supportive treatment alone resulted in an ICER of £277,000 per QALY gained for patients in FC III and £343,000 per QALY gained for patients in FC IV.

The reference case for iloprost plus supportive treatment compared with supportive treatment alone resulted in an ICER of £101,000 per QALY gained.

The reference case for bosentan plus supportive treatment compared with supportive treatment alone resulted in an ICER of £27,000 per QALY gained.

The reference case for sitaxentan plus supportive treatment compared with supportive treatment alone resulted in an ICER of £25,000 per QALY gained.

In general, sildenafil plus supportive treatment was more effective and less costly than supportive treatment alone and therefore dominated supportive treatment.

Discussion

All five technologies (intravenous epoprostenol, inhaled iloprost, bosentan, sitaxentan and sildenafil), when added to supportive treatment and used at their licensed doses, have been shown to be more clinically effective than supportive treatment alone, in RCTs that included patients of mixed FC and mixed subtypes of PAH. The volume of evidence and the patient populations included in the trials varied among the technologies. The Assessment Group felt that current evidence did not allow adequate comparisons between the technologies, nor for the use of combinations of the technologies. All intervention therapies alongside supportive treatment led to a QALY improvement compared with supportive treatment alone; however the cost-effectiveness ratios vary considerably.

Considerable uncertainties were reported by the Assessment Group. Uncertainties mainly derived from the lack of long-term data from RCTs with regard to how long treatment effects last and whether they differ significantly for patients in different FCs and, if so, to what extent. Comparisons between the technologies were not planned by the Assessment Group, and were not considered appropriate given currently available evidence.

The ICERs for bosentan, sitaxentan and sildenafil (but not iloprost) depend to some extent on the cost of epoprostenol. As epoprostenol is assumed to be the treatment of choice when patients deteriorate to FC IV, those patients receiving supportive care will on average go on to epoprostenol earlier than patients on the technologies. Thus the time spent on epoprostenol will vary among the technologies, and the total cost attributable to epoprostenol will also vary. The unit cost of epoprostenol can therefore influence the ICER of the compared technologies. Iloprost is a lot more expensive than the oral drugs and results in a much reduced QALY difference – patients are progressing to FC IV faster than those on oral therapies, but slightly slower

than those on supportive treatment. Therefore, the price of epoprostenol has an impact on the cost of both the technology arm and the supportive treatment arm.

4 Issues for consideration

4.1 Clinical effectiveness

The findings for clinical effectiveness may have minimal impact on clinical practice as these technologies are already being used in NHS. However the following points should be considered.

4.1.1 Patient population

Evidence is generally provided on mixed populations of different PAH subcategories and/or FC, and therefore is not directly related to the licensed indication of individual technologies. Is the use of data from the clinical trials examining the clinical effectiveness in categories of PAH that do not match the licence indication appropriate?

Current evidence does not allow adequate comparisons between the technologies, or for the use of combinations of the technologies. This means that a decision for each drug will have to be made individually in this appraisal.

4.1.2 Generalisability

Are the results of the clinical trials generalisable to the patient population of England and Wales given the number of trials presented that have been conducted in countries other than the UK?

Most RCTs excluded patients with unstable conditions. The patients who are seen in clinical practice may be sicker than those included in the trials. The implication for the generalisability of the findings is uncertain. Does the Committee believe that the results of the trials excluding patients with unstable conditions are generalisable?

4.1.3 Economic evaluation

There was no consensus in the manufacturers' submissions on the most appropriate model structure for the technology assessment. It may not be appropriate to compare the manufacturers' models with the Assessment Group model as they address different questions. As a result, should the estimates of cost effectiveness be taken from the manufacturer evaluations or the Assessment Group model?

4.1.4 Key model assumption

The cost effectiveness of oral drugs for PAH in the Assessment Group model generally relies on the assumption that epoprostenol is recommended for FC IV and that all patients who move to FC IV are given epoprostenol. The cost effectiveness of the oral drugs in particular is then based on delaying patients' movement to FC IV, resulting in reduced costs of epoprostenol. In addition, the models assume that in FC IV patients will stop all other treatments and receive epoprostenol.

Is the above assumption valid? Is epoprostenol likely to be given alone in patients moving to FC IV in clinical practice or are other treatments also given?

4.1.5 Prices of technologies

The cost of drugs used in the Assessment Group model reference case may not reflect those used in clinical practice. It is difficult to accurately calculate these costs as centres can negotiate individually with some manufacturers on drug price. This point refers mainly to the cost of epoprostenol. In the Assessment Group model, when the varying prices of epoprostenol are used, this affects the cost effectiveness of the oral drugs considered in the analysis. What is the real cost of these technologies to the NHS? In addition, should service provision such as home care be taken into consideration?

4.1.6 Uncertainty

In light of the paucity of data and consequent large number of assumptions made in the economic modelling, is there too much uncertainty to make an accurate decision on the cost effectiveness of these drugs?

The findings from the economic evaluation suggest that epoprostenol and iloprost may not be cost effective. Withdrawal of these technologies, however, could have substantial impact on patients who are currently treated with them, and could also raise ethical issues. Any changes in costs for epoprostenol and/or licensing of new treatment for patients in FC IV could have an impact on the cost effectiveness of the other technologies.

5 Ongoing research

The European Society for Cardiology (ESC) and the American College of Chest Physicians are believed to be updating their current guidelines for 2008.

6 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report for this appraisal was prepared by the West Midlands Health Technology Assessment Collaboration.

- Dr Chen Y-F et al. Clinical and cost-effectiveness of treatments for pulmonary arterial hypertension (PAH) within their licensed indications, August 2007.

B The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope and the assessment report. Organisations listed in I and II were also invited to make written submissions.

I Manufacturers/sponsors:

- Actelion Pharmaceuticals UK Ltd
- Encysive (UK) Ltd
- GlaxoSmithKline
- Pfizer Ltd
- Schering Health Care Ltd

II Professional/specialist and patient/carer groups:

- Royal College of Physicians } These groups submitted
- British Cardiovascular Society } their responses jointly
- British Society for Rheumatology
- Pulmonary Hypertension Association UK
- Raynaud's & Scleroderma Association
- Royal College of Nursing
- London Specialised Commissioning Group } These groups
- South Staffordshire Primary Care Trust } submitted
- West Midlands Specialist Commissioning Group } their responses jointly

III Commentator organisations (without the right of appeal):

- None received

Appendix B: Summary of clinical trial data included in the assessment report

Distribution of comparisons undertaken in RCTs

	Epoprostenol	Iloprost	Bosentan	Sitaxentan	Sildenafil	Bosentan + epoprostenol	Iloprost + (ongoing) bosentan	Sildenafil + (ongoing) epoprostenol
Placebo/ existing treatment	3 Rubin 1990 Barst 1996 Badesch 2000	2 Olschewski 2002 (AIR) unpublished (AIR-2)	4 Channick 2001, Rubin 2002 (BREATHE-1) Galie 2006 (BREATHE-5) Barst 2006 (STRIDE-2)	3 Barst 2004 (STRIDE-1) Barst 2006 (STRIDE-2) Barst 2007 (STRIDE-4)	4 Galie 2005 (SUPER-1) Bharani 2003 Sastry 2004 Singh 2006	0	0	0
Epoprostenol*	n/a	0	0	0	0	1 Humbert 2004 (BREATHE-2)	0	1 Unpublished (PACES-1)
Iloprost	n/a	n/a	0	0	0	0	0	0
Bosentan**	n/a	n/a	n/a	1 Barst 2006 (STRIDE-2)	1 Wilkins 2005 (SERAPH)	0	2 Hoeper 2006 (COMBI) McLaughlin 2006 (STEP)	0
Sitaxentan	n/a	n/a	n/a	n/a	0	0	0	0
Sildenafil	n/a	n/a	n/a	n/a	n/a	0	0	0

*Newly initiated for BREATHE-2, ongoing for PACES-1 **Newly initiated for STRIDE-2 and SERAPH, ongoing for COMBI and STEP

Summary table of the clinical trials identified in the Assessment Report

Trial name	Study design	Length of follow-up	N	Type of PAH	Intervention	Comparator	Functional class	Primary endpoint	Secondary endpoint
Epoprostenol									
Rubin 1990	Open-label, parallel; 4 centres, USA	8 weeks	23	PPH (100%)	Epoprostenol (iv infusion) individualised dose (n=11)	None (n=12)	II (9%) III (65%) IV (26%)	Cardiopulmonary haemodynamics	Exercise capacity Adverse events
Barst 1996	Open-label, parallel, multicentre, USA	12 weeks	81	PPH (100%)	Epoprostenol (iv infusion) individualised dose (n=41)	None (n=40)	III (74%) IV (26%)	Exercise capacity	Survival Quality of life, Cardiopulmonary haemodynamics, NYHA functional class
Badesch 2000	Open-label, parallel; 17 centres, USA	12 weeks	111	Scleroderma spectrum of disease (100%)	Epoprostenol (iv infusion) individualised dose (n=56)	None (n=55)	II (5%) III (78%) IV (17%)	Exercise capacity	Cardiopulmonary haemodynamics, Borg Dyspnoea score, Dyspnoea-fatigue rating, NYHA functional class, digital ulcers, Raynaud's phenomenon severity score, safety, survival, adverse events
Iloprost									
AIR / Olschewski 2002 (A02997)	Double-blind, parallel, 37 centres, Europe	12 weeks	203	PPH (50%), collagen vascular disease (17%), appetite suppressant (4%), non-PAH (28%)	Iloprost (inhalation) 2.5 or 5.0 µg six or nine times daily (n=101)	Placebo (inhalation) (n=102)	III (59%) IV (41%)	Composite end point – at least 10% increase in 6MWD and improvement in FC without deterioration	6MWD, NYHA class, survival, haemodynamics, quality of life
AIR-2 (A02237)	Open-label, parallel, multicentre Germany	12 weeks	63	PPH (63%), [redacted]	Iloprost (inhalation) 24 µg daily divided into six or nine doses (n=30)	None (n=33)	II (33%) III (48%) IV (19%)	safety, survival, NYHA class, quality of life	NS
COMBI / Hoeper 2006	Open-label, parallel; multicentre Germany,	12 weeks	40	IPAH (100%)	Iloprost (inhalation) 5 µg six times daily + ongoing bosentan (oral) 125 mg bd (n=19)	Ongoing bosentan (oral) 125 mg bd (n=21)	III (100%)	6MWD	Haemodynamics
STEP / McLaughlin 2006	Double-blind, parallel, multicentre, USA	12 weeks	67	IPAH (55%), associated PAH including scleroderma, other connective tissue diseases, repaired congenital heart disease, HIV infection and anorexigen use (45%)	Iloprost (inhalation) 5 µg six to nine times daily + ongoing bosentan (oral) 125 mg bd (n=34)	Placebo + ongoing bosentan (oral) 125 mg bd (n=33)	II (1.5%) III (94%) IV (4.5%)		

Trial name	Study design	Length of follow-up	N	Type of PAH	Intervention	Comparator	Functional class	Primary endpoint	Secondary endpoint
Bosentan									
Channick 2001 (AC-052-351)	Double-blind, parallel; USA & France, 6 centres	12 weeks;	32	PPH (84%), scleroderma (16%)	Bosentan (oral) 125 mg bd e (n=21)	Placebo (n=11)	III (100%)	Exercise capacity at week 12, measured by the distance walked by in 6 minutes (6MWT)	Cardiopulmonary haemodynamics (pulmonary vascular resistance [PVR], cardiac index, mean pulmonary artery pressure, mean right atrial pressure, pulmonary capillary wedge pressure) Withdrawal because of clinical worsening Borg Dyspnoea score WHO functional class Safety parameters
BREATHE-1 / Rubin 2002	International, 27 centres	16 weeks	213	PPH (70%), CTD (30%)	Bosentan (oral) 125 mg bd e (n=74), 250 mg bd e (n=70)	Placebo (n=69)	III (92%) IV (8%)	Change in exercise capacity (measured by the 6MWT)	Change in Borg Dyspnoea score Change in WHO functional class Time from randomisation to clinical worsening (defined as the combined end point of death, lung transplantation, hospitalisation for pulmonary hypertension, lack of clinical improvement or worsening leading to discontinuation, need for epoprostenol therapy, or atrial septostomy).
BREATHE-5 / Galiè 2006	Double-blind, parallel double-blind, parallel; international, 15 centres	16 weeks;	54	Eisenmenger syndrome (100%)	Bosentan (oral) 125 mg bd e (n=37)	Placebo (n=17)	III (100%)	Safety: systemic arterial blood oxygen saturation Pulmonary vascular resistance (PVR) – primary efficacy endpoint	Exercise capacity assessed by the 6MWT Additional haemodynamic parameters WHO functional class
STRIDE-2 (FPH02) / Barst 2006	Double-blind (open-label for bosentan), parallel international, 55 centres	18 weeks;	247	IPAH (59%), CTD (30%), congenital heart disease (11%)	Bosentan (oral) 125 mg bd e (n=60); sitaxentan (oral) 50 mg od (n=62), 100 mg od (n=61)	Placebo (n=62)	II (37%) III (59%) IV (4%)	change from baseline in 6MWD at week 18	Change in WHO FC, time to clinical worsening, and change in Borg Dyspnoea score
Bosentan + epoprostenol vs. epoprostenol									
BREATHE-2 / Humbert 2004	USA & Europe, 7 centres	16 weeks; double-blind, parallel	33	PPH (82%), CTD (18%)	Bosentan (oral) 125 mg bd e + epoprostenol (iv infusion) started with 2 ng/kg/min and increased to 12-16	Placebo + epoprostenol (iv infusion) started with 2 ng/kg/min and	III (76%) IV (24%)	Total pulmonary resistance (TPR)	Other haemodynamic parameters (including cardiac index, PVR) Exercise capacity WHO functional class

Trial name	Study design	Length of follow-up	N	Type of PAH	Intervention	Comparator	Functional class	Primary endpoint	Secondary endpoint
					ng/kg/min between week 14 and 16 (n=22)	increased to 12-16 ng/kg/min between week 14 and 16 (n=11)			
SERAPH / Wilkins 2005	Double blind, parallel.	16 weeks	26	IPAH (88%), CTD (12%)	Bosentan (oral) 125mg bd (n=12)	Sildenafil (oral) 50mg tid (n=14)	III (100%)	Right ventricular mass, measured by Computerised Magnetic Resonance imagining (CMR)	Change in 6MWD from baseline, change in cardiac index from baseline, change from baseline in breathlessness symptoms using the Borg dyspnoea score, quality of life, plasma B-type natriuretic peptide (BNP) levels.
Sitaxentan									
STRIDE-1 (FPH01) / Barst 2004	double-blind, parallel USA & Canada, 23 centres	12 weeks;	178	IPAH (53%), CTD (24%), congenital S-P shunts (24%)	Sitaxentan (oral) 100 mg od (n=55), 300 mg od (n=63)	Placebo (n=60)	II (33%) III (66%) IV (1%)	Change from baseline to week 12 in percent of predicted peak oxygen uptake (VO2)	6-minute walk distance (6MWD) NYHA FC VO2 at anaerobic threshold (AT) Haemodynamic parameters (Ppa, mean arterial pressure, cardiac index and pulmonary vascular resistance) Quality of life (as measured by the Medical Outcomes Study Short Form 36) Time to events of clinical worsening (defined as death, epoprostenol use, arterial septostomy or transplantation).
STRIDE-2 (FPH02) / Barst 2006	Double-blind (open-label for bosentan), parallel international, 55 centres	18 weeks	247	IPAH (59%), CTD (30%), congenital heart disease (11%)	Bosentan (oral) 125 mg bde (n=60); sitaxentan (oral) 50 mg od (n=62), 100 mg od (n=61)	Placebo (n=62)	II (37%) III (59%) IV (4%)	Change from baseline in 6MWD at week 18	Change in WHO FC, time to clinical worsening, and change in Borg Dyspnoea score
STRIDE-4 (FPH04) / Barst 2007	Double-blind, parallel Latin America, Poland, Spain	18 weeks;	98	IPAH (68%), CTD (15%), congenital heart disease (16%)	Sitaxentan (oral) 50 mg od (n=32), 100 mg od (n=32)	Placebo (n=34)	II (61%) III (38%) IV (1%)	Change from baseline in 6MWD	NS
Sildenafil									
SUPER-1 (A1481140) / Galiè 2005	Double-blind, parallel international, 53 centres	12 weeks;	278	IPAH (63%), CTD (30%), repaired congenital S-P shunts (6%)	Sildenafil (oral) 20 mg tid (n=69), 40 mg tid (n=67), 80 mg tid (n=71)	Placebo (n=70)	I (0.4%) II (39%) III (58%) IV (3%)	Exercise capacity, as measured by the 6-minute walk test	Mean pulmonary artery pressure (PAP) Time to clinical worsening Borg Dyspnoea score Tertiary outcomes Pulmonary hypertension Criteria for

Trial name	Study design	Length of follow-up	N	Type of PAH	Intervention	Comparator	Functional class	Primary endpoint	Secondary endpoint
									functional capacity and therapeutic class Change in chronic use of background therapy for PAH Quality of life
Bharani 2003	Double-blind, cross-over	2 x two weeks (with washout period of ≥2 weeks);	10	PPH (30%), Eisenmenger syndrome (30%), non-PAH (30%)	Sildenafil (oral) 25 mg tid	Placebo	II (33%) III (56%) IV (11%)	NS	NS
Sastry 2004	Double-blind, cross-over India, single centre	2 x 6 weeks (no washout period)	22	PPH (100%)	Sildenafil (oral) 25 – 100 mg tid depending on body weight (n=10 receiving sildenafil first)	Placebo (n=12 receiving placebo first)	II (82%) III (18%)	exercise capacity, as measured by the 6-minute walk test	NS
Singh 2006	Double-blind, cross-over India, single centre	2 x 6 weeks with a two-week washout;	20	IPAH (50%), Eisenmenger Syndrome (50%)	Sildenafil (oral) 25 – 100 mg tid depending on body weight	Placebo	II (40%) III (55%) IV (5%)	NS	NS
Sildenafil vs. placebo with ongoing epoprostenol and supportive treatment									
PACES-1 (A1481141),	Double-blind, parallel international, multicentre	16 weeks	267	PPH (79%), CTD (21%)	Sildenafil (oral) started 20 mg tid, titrated up to 80 mg tid by week 8 if tolerated + ongoing epoprostenol (individualised optimal dose) (n=134)	Placebo + ongoing epoprostenol (individualised optimal dose) (n=133g)	N=257 I (1%) II (26%) III (67%) IV (5%)	Exercise capacity, as measured by the 6-minute walk test	Mean pulmonary artery pressure (mPAP) Time to clinical worsening Borg Dyspnoea score Tertiary outcomes Pulmonary hypertension Criteria for functional Capacity and therapeutic class Quality of life Patient overall preference Assessment Change in chronic use of background therapy

NS – not specified in the manufacturer's submission or Assessment Report