

Clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for pulmonary arterial hypertension within their licensed indications: a systematic review and economic evaluation

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Executive summary

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Executive summary

Background

Pulmonary arterial hypertension (PAH) is a diverse group of diseases with similar pathophysiology and clinical presentation. It is characterised by a progressive increase of pulmonary vascular resistance, leading to right ventricular heart failure and premature death. PAH can occur with no identifiable cause. This was previously referred to as primary pulmonary hypertension (PPH) but was renamed as idiopathic PAH (IPAH). PAH is also commonly associated with various conditions including connective tissue disease (CTD-APAH) and congenital heart disease (CHD). Symptoms of PAH include dyspnoea (breathlessness), fatigue, chest pain, syncope (fainting) and oedema, which can result in loss of capacity to perform exercise and eventually activity of daily living. It therefore has a devastating impact on both the quality and duration of patients' life. PAH is a rare disease with an estimated incidence of two to four cases per million per year, which approximates 100 to 200 new cases in England and Wales per year.

Until the 1990s, PAH was managed by supportive treatments, which include anticoagulation therapy, diuretics, oxygen and digoxin that mainly aim at controlling symptoms. In addition, calcium channel blockers (CCBs) were found to be effective for treating a small proportion of patients with PAH. More recently, new technologies specifically licensed for treating PAH have become available in the UK. These include intravenous epoprostenol, inhaled iloprost, and three oral treatments: bosentan, sitaxentan and sildenafil. The licenses differ between the technologies in terms of type of PAH and severity of disease measured by functional class (FC). These technologies are believed to not only relieve symptoms but also to potentially modify disease progress. Once initiated the technologies are given repeatedly and only when inevitably the disease progresses are additional treatments or (more rarely) switching considered. The costs for these technologies vary but are very high (≈£12–£400 per patient per day, list price of drug only).

Objectives

The objectives of the assessment report were:

- To assess as far as available data from randomised controlled trials (RCTs) would allow, whether the five technologies named above (alone or in combination) are clinically effective when used within their licensed indications for the treatment of adults with PAH for whom CCBs are inappropriate or no longer effective compared to supportive treatment (and/or intravenous iloprost), and whether the clinical effectiveness differs significantly between PAH of various causes.
- To assess whether the clinical effectiveness differs significantly between the technologies (alone or in combination) if head-to-head RCTs exist.
- To assess whether each of the five technologies are cost-effective when used within their licensed indications for treating adults with PAH for whom CCBs are inappropriate or no longer effective compared to supportive treatment.

Methods

Clinical effectiveness

A systematic review of RCTs was undertaken. Databases searched included the Cochrane Library, MEDLINE, and EMBASE along with other sources up to February 2007. Further data were obtained from dossiers submitted to the National Institute for Health and Clinical Excellence (NICE) by the manufacturers of the technologies. RCTs of longer than one week duration that compared any of the five technologies (alone or in combination) to placebo, supportive care, any other technologies (alone or in combination) and/or non-licensed drugs in adult PAH patients were included. Inclusion decisions, quality assessment and data extraction were undertaken according to predefined criteria. Where sufficient data were available, meta-analyses were undertaken for each technology using a random effects model. Primary analysis included data from FCIII patients (and FCIV patients for epoprostenol) for licensed doses only. Extensive sensitivity analyses were carried out.

Cost-effectiveness

A systematic review of published studies on the costs and cost-effectiveness of the technologies in PAH, and a review of the dossiers submitted to NICE by the manufacturers of the technologies were undertaken. In addition, model-based economic evaluations of

the cost-effectiveness of the technologies from the perspective of the UK National Health Service (NHS) and Personal Social Service (PSS) were carried out.

Results

Clinical effectiveness and cost-effectiveness

A total of 20 RCTs, most of good quality, were included in this assessment. The majority had durations of 12 to 18 weeks and compared one of the technologies added to supportive treatment versus supportive treatment alone. Only a small number of trials compared the technologies against each other or investigated the use of combinations of technologies.

Many of the trials included patient populations (in terms of FC and types of PAH) and doses that were outside the licensed indication of the technologies. Only very limited data examining specific types (subcategories) of PAH were available. Existing data do not suggest significant differences in treatment effects between subcategories of PAH, but studies are likely to be under-powered to detect clinically important differences.

Data stratified by FC were scant, as such an assessment of treatment effects stratified by FC could not be reliably conducted with the available evidence. This is particularly problematic when findings from the clinical effectiveness review were to be used to inform the economic modelling.

Monotherapy added to supportive treatment versus supportive treatment

All the technologies, when added to supportive treatment at their licensed doses, have been shown to be more effective than supportive treatment alone in improving exercise capacity, symptoms of PAH and haemodynamic measures. The volume of evidence and patient populations included in the trials varied between technologies. The incremental cost-effectiveness ratio (ICER) for each technology added to supportive treatment compared to supportive treatment varies considerably between the technologies according to the independent economic evaluation conducted for this report.

The effectiveness of intravenous epoprostenol has been shown in open-label RCTs that included both patients with PPH and patients with scleroderma. Pooled results for PPH patients with mixed FC (mainly III & IV, licensed indication) for improvement in 6-minute walk distance (6MWD) was 58 metres

(95% confidence interval 6 to 110) and the odds ratio (OR) for FC deterioration at 12 weeks was 0.40 (0.13 to 1.20) compared to supportive care. Independent economic evaluation gave ICERs for the reference case for epoprostenol plus supportive care compared to supportive care alone of £277,000/quality-adjusted life-year (QALY) for FCIII and £343,000/QALY for FCIV patients. In non-reference case analyses the lowest of these ICERs became £106,000/QALY and £96,000/QALY respectively when the manufacturer's reduced price was used. Most other non-reference case analyses did not appreciably alter the magnitude of the reference case ICERs.

The effectiveness of inhaled iloprost has been shown in one double-blind RCT that included patients of mixed FC (III and IV) with mixed types of pulmonary hypertension including non-PAH. For FCIII PPH patients (licensed indication), stratified data for 6MWD were not available and OR for deterioration in FC at 12 weeks was 0.29 (0.07 to 1.18) compared to supportive care. An additional open-label RCT demonstrated effectiveness in only some of the measured outcomes. Independent economic evaluation gave an ICER for the reference case for iloprost plus supportive care compared to supportive care alone of £101,000/QALY. Non-reference case analyses did not appreciably reduce the magnitude of this ICER.

The effectiveness of bosentan was demonstrated in double-blind RCTs that included patients predominantly of FC III and an additional open-label RCT. Effectiveness has been shown in mixed populations of IPAH, CTD-APAH and PAH associated with Eisenmenger syndrome, a specific type of CHD. For FCIII patients with mixed PAH (licensed indication), the pooled result for improvement in 6MWD was 59 metres (20 to 99) and the pooled OR for deterioration in FC at 12 weeks was 0.21 (0.03 to 1.76) compared to supportive care. Independent economic evaluation gave an ICER for the reference case for bosentan plus supportive care compared to supportive care alone of £27,000/QALY. Non-reference case analysis demonstrated the ICER was sensitive to running the model over a shorter time horizon and with a lower cost of epoprostenol.

The effectiveness of sitaxentan was demonstrated in double-blind RCTs that included patients of mixed FC (predominantly II and III) with mixed PAH (IPAH, CTD-APAH and PAH associated with CHD). For FCIII patients with mixed PAH (licensed indication), no stratified data for improvement in 6MWD were available and the pooled OR for deterioration in FC at 12 weeks was 0.18 (0.02 to 1.64) compared to supportive care. Independent economic evaluation

gave an ICER for the reference case for sitaxentan plus supportive care compared to supportive care of £25,000/QALY. Non-reference case analysis demonstrated the ICER was sensitive to running the model over a shorter time horizon and with a lower cost of epoprostenol.

The effectiveness of sildenafil was demonstrated in a double-blind RCT that included patients of mixed FC (predominantly II and III) with mixed PAH (IPAH, CTD-APAH and PAH associated with CHD). For FCIII patients with mixed PAH (licensed indication), no stratified data for improvement in 6MWD were available and the OR for deterioration in FC at 12 weeks was [confidential information removed] compared to supportive care. Independent economic evaluation demonstrated that for the most part sildenafil plus supportive care was more effective and less costly than supportive care alone and therefore dominated supportive care. Even when sildenafil did not dominate ICERs were on the whole still relatively low.

Direct comparison

Only two RCTs have directly compared the technologies against each other. No significant difference between the technologies was observed in any outcome in both trials. However, the conclusion was limited by small sample size in one trial and differential blinding of treatments in the other trial. No independent economic analysis was undertaken for this comparison.

Combination therapy

Use of the combinations of the technologies was investigated in four RCTs. A double-blind RCT showed no benefit for using the combination of bosentan plus epoprostenol compared to epoprostenol alone in patients of mixed FC (III and IV) with mixed types of PAH (IPAH, CTD-APAH).

A double-blind RCT showed that inhaled iloprost added to ongoing bosentan and supportive treatment was more effective than ongoing bosentan and supportive treatment in patients (mainly FCIII) with mixed types of PAH. However, a further open-label RCT that included patients of FCIII with IPAH failed to demonstrate this.

A double-blinded RCT showed that above licensed doses of sildenafil added to ongoing epoprostenol and supportive care was more effective than ongoing epoprostenol and supportive care in patients of mixed FC (predominantly II and III) with mixed types of PAH (IPAH and CTD-APAH).

No independent economic analyses were undertaken for these comparisons.

Comment on independent economic evaluation

The ICERs for one technology should not be compared to that of another technology as the model only compares each technology plus supportive care to supportive care alone. To do so would be inappropriate.

In the model epoprostenol treatment is initiated on progression to FCIV, as such the ICERs for all technologies are sensitive to the cost of epoprostenol.

Due to the lack of stratified data to populate the model, and in some cases a complete absence of data, a number of assumptions had to be made, therefore bias may have been introduced by these assumptions. In addition, the data used for the model were mostly from trials of short duration containing relatively small numbers of patients. Therefore a longitudinal dataset of a sufficient number of patients would be of great benefit to future modelling in this clinical condition.

Due to the above, the probabilistic sensitivity analysis undertaken in this report may well have underestimated the full uncertainty around each analysis.

Published economic evaluations

Four published economic evaluations were identified. None produced results generalisable to the NHS.

Review of economic evaluations submitted by manufacturers

There was no consensus in the manufacturers' submissions on the most appropriate model structure for the technology assessment, with variability seen in the type of economic evaluation, methods used and data sources. In addition, the same comparator was not used in all submissions therefore they were not all addressing the same policy question.

Discussion

Strengths, limitations of the analyses and uncertainties

The strengths of this assessment report include a systematic review focusing on the most robust evidence from RCTs, comprehensive literature search, inclusion of unpublished data, comprehensive analyses highlighting the mismatch between licensed

indications and available evidence, independent assessment of published economic evaluations and manufacturer submissions, a de novo model-based economic evaluation, and use of data from the systematic review to inform the model.

The analyses included in this report were restricted by the scope of the technology appraisal, which was to include only licensed indications for the technologies currently licensed in the UK. The analyses were also limited by the short duration of RCTs and the paucity of data stratified by types of PAH and FC. Uncertainties mainly derive 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 FC and to what extent. Comparisons between the technologies were not planned, and were not considered appropriate given available evidence.

Generalisability of the findings

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. Variations in the costs of the technologies (including services) between regions/centres inevitably affect the cost-effectiveness of these technologies. Furthermore, the economic modelling suggested the cost-effectiveness of the technologies is sensitive to the costs of epoprostenol.

Conclusions

All the five technologies, when added to supportive treatment and used at licensed dose(s), have been shown to be more effective than supportive treatment alone in RCTs that included patients of mixed FC and types of PAH. The volume of evidence and patient populations included in the trials varied between the technologies. Current evidence does not allow adequate comparisons between the technologies nor for the use of combinations of the technologies.

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

Implications for service provision

The findings for clinical effectiveness have minimal impact on clinical practice as these technologies are already being used in NHS. The findings from

the economic evaluation suggest the possibility of differential cost-effectiveness between the oral treatments. This requires further confirmation as current analysis was not designed for directly comparing the technologies. If confirmed, the use of the most cost-effective treatment would result in reduction in costs for the NHS.

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 FCIV patients could have impact on the cost-effectiveness of the other technologies.

Suggested research priorities

Long-term, double-blind RCTs of sufficient sample size that directly compare bosentan, sitaxentan and sildenafil, and evaluates outcomes including survival, quality of life, maintenance on treatment and impact on the use of resources for NHS and personal social services are needed. Possible differences in treatment effects between subcategories of PAH and between patients of different FC at baseline should be investigated within and across these trials.

More RCTs that evaluate combinations of the technologies versus monotherapy, and studies investigating the feasibilities of replacing an ongoing treatment that failed to provide adequate control of the disease with a new treatment rather than adding the new treatment to the existing treatment are required.

Further methodological studies that investigate the predictive value of outcome measures such as 6MWD, FC, various haemodynamic measures and other novel measures on patients' prognosis and survival are needed. The reason for substantial variation in patient's responses seen in control groups in RCTs also needs to be established.

Publication

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NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

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The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

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