Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence – Drugs for the treatment of pulmonary arterial hypertension

Final protocol (19 February 2007, submitted to NCCHTA/NICE)

1. Title of the project

Clinical and cost effectiveness of epoprostenol, iloprost, bosentan, sitaxentan, and sildenafil for the treatment of pulmonary arterial hypertension in adults: a systematic review and economic evaluation

2. Name of the TAR team and 'lead'

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3. Plain English Summary

Pulmonary arterial hypertension (PAH) is a rare, progressive but severe condition. It involves elevated pressure in the arteries that carry blood from right heart to the lung. PAH may occur without any identifiable reasons (idiopathic PAH). It may also be associated with a diverse group of diseases such as certain diseases of the collagen tissues and congenital heart disease. If not treated, PAH leads to heart failure and eventually death.

Various interventions have been used to treat patients with PAH. Some of them are for treating symptoms and conditions that are frequently associated with PAH, such as diuretics (water tablets) for swelling of limbs, anticoagulants for preventing clots in the blood vessels, inhaled oxygen to increase oxygen level in the blood, and digoxin to strengthen heart beats. As these treatments do not alter the elevated blood pressure in the lung, they are regarded as 'supportive treatments'. In addition, a group of drugs called calcium channel blockers, which are used to treat hypertension, have been found to work in a minority of patients with PAH.

More recently, newer drugs have been developed that target at different potential mechanisms underlying the development of PAH. Five of these drugs have been licensed in the UK; epoprostenol, iloprost, bosentan, sitaxentan and sildenafil.

The aim of this technology assessment is to evaluate whether these five drugs are effective for treating PAH, and whether the use of these drugs in addition to

supportive treatments is cost-effective (good value for money) for the National Health Services (NHS). The key components of the report are:

- A systematic review of randomised controlled trials (RCTs) that investigated the effectiveness of these drugs in PAH. Variations in the effectiveness between the drugs and/or between different PAH populations will be explore if evidence from RCTs permits.

- A systematic review of published studies on the costs and cost-effectiveness of these drugs in PAH.

- A review of the dossiers submitted to the National Institute for Health and Clinical Excellence (NICE) by the manufacturers (GlaxoSmithKline, Schering Health Care, Actelion Pharmaceuticals, Encysive and Pfizer).

- A focused, model-based economic evaluation. This involves the use of mathematical and statistical methods to synthesise information on treatment costs and the impact of the treatments on patients' quality and duration of life.

4. Decision problem

4.1 Decision to be made

According to the final scope issued by the National Institute for Health and Clinical Excellence (NICE) for this technology appraisal, the decisions to be made are:

- Whether epoprostenol, iloprost, bosentan, sitaxentan and sildenafil, when used within their licensed indications, are clinically effective and cost effective compared to supportive treatments (see section 4.4) in adults with PAH for whom calcium channel blockers are inappropriate or no longer effective.

- Whether the interventions being considered are clinically more effective, or more cost-effective, in patients with certain subcategories of pulmonary arterial hypertension according to Venice 2003 clinical classification (see Appendix 1).

- Whether significant differences in clinical and cost effectiveness exist between the interventions being considered (either used alone or in combination) when compared to each other and/or intravenous iloprost.

It is likely that the assessment report will be able to address only some of the issues surrounding these decision problems for the following reasons:

(1) While the Venice 2003 clinical classification provides a significantly improved framework for the diagnosis and management of PAH, it is worth highlighting that patients with PAH represent diverse populations that vary greatly in aetiology, disease progression, and prognosis. Cases being grouped under each of the Venice subcategories can still be heterogeneous in term of severity, the choice and response to treatment and prognosis. For example, within the Venice subcategory 1.3.1, scleroderma has distinct features that may warrant it being considered separately from other forms of connective tissue diseases.

(2) The five interventions being considered in this technology appraisal have different routes of administration, demand on patients' self-management, speediness of action, adverse effect profile and contraindications. The selection of treatments is highly dependent on the nature of the underlying condition, clinical circumstances and patient ability and acceptance. The choice of treatment and appropriate comparators will therefore be dependent on these factors.

(3) PAH is a rare condition. The number of patients included in clinical studies is relatively small. There is unlikely to be sufficient data to allow meaningful comparison between many of the subcategories of PAH and between different treatments (or combinations of treatments).

Bearing these in mind, the assessment group intends to undertake a systematic review of randomised controlled trials (RCTs) and a review of industry submissions to establish the underlying evidence base that is available to answer the above decision problems and to highlight issues that are unlikely to be addressed due to paucity of evidence. A model-based economic evaluation will then be carried out to address refined and focused decision problem(s) that take into account the availability of evidence, the appropriateness of combining different populations of PAH in terms of underlying cause (e.g. whether the model can include all PAH populations or the modelling can be reasonably done only for a specific population according to the evidence), disease severity (e.g. it may be necessary to model patients in functional class III and IV separately), and the most appropriate place in the treatment pathway for each of the interventions being considered (e.g. oral treatments would not be considered as alternative, competing interventions against intravenous epoprostenol for patients in NYHA/WHO functional class IV).

4.2 Population and relevant subgroups

The population being considered is adults with pulmonary arterial hypertension (Category 1 of the Venice 2003 clinical classification, see Appendix 1) in NYHA/WHO functional classes III (and also functional class IV for epoprostenol) for whom calcium channel blockers are inappropriate or no longer effective.

Potentially relevant subgroups include:

- PAH associated with specific disease conditions (e.g. scleroderma) or subcategories of PAH (e.g. idiopathic PAH) under Category 1 of the Venice 2003 clinical classification. These are better perceived as different patient populations that share similar clinical manifestations of PAH than 'subgroups' of a well characterised disease.
- NYHA/WHO functional classes.

As suggested earlier, the identification of specific subgroups to be examined (e.g. patients with idiopathic PAH in functional class III) will be undertaken in light of current treatment guidelines and consultation with our clinical advisors, taking into account the volume of available evidence and resources available for this technology assessment.

4.3 Definition of the interventions

For patients in functional class III, interventions being considered are:

- Epoprostenol (Folan®, GlaxoSmithKline), administered by continuous intravenous infusion
- Iloprost (Ventavis®, Schering Health Care), administered by inhalation through a nebuliser, 2.5 micrograms to 5.0 micrograms as delivered at the mouthpiece per inhalation session)
- Bosentan (Tracleer®, Actelion Pharmaceuticals), administered orally, 62.5 mg to 250 mg twice daily
- Sitaxentan (Thelin®, Encysive), administered orally, 100 mg once daily
- Sildenafil (Revatio®, Pfizer), administered orally, 20 mg three times daily*

Epoprostenol administered by continuous intravenous infusion is the only intervention being considered for patients in functional class IV.

4.4 Relevant comparators

- *Supportive treatments*: these include digoxin, diuretics, anticoagulants and oxygen.

- *Placebo or no treatment*: whilst the above supportive treatments are used for preventing/treating conditions and symptoms associated with PAH, the goals and mechanisms of these treatments are generally different from those of the interventions being considered here. As these supportive treatments usually start earlier in the treatment pathway and are usually continued when introducing the newer interventions, studies in which the interventions were compared to placebo or no treatment are clinically relevant provided that supportive treatments were continued in all study arms.

- The interventions being considered, either used alone or in combination, will be compared with each other if evidence is available from randomised controlled trials (RCTs).

- Intravenous iloprost may be considered as a comparator if evidence is available from RCTs.

* Clarification is required with regard to whether Viagra® can be regarded as an intervention instead of Revatio® for the purpose of cost reduction.

4.5 Place of the intervention in the treatment pathway(s)

Based on the final scope, the interventions being considered are to be used when conventional supportive treatments and calcium channel blockers are either inappropriate or have failed to control symptoms and maintain functional capacity.

For this technology assessment, only the first use of listed interventions will be considered. Use of any of the interventions after failure of another listed intervention will not be considered (epoprostenol for patients in functional class IV may be an exception).

4.6 Key factors to be addressed (e.g. clinical and cost outcomes, further considerations, problematic factors)

Key outcomes

The key outcomes, among other outcomes to be examined (see section 5.3), for the technology assessment include improvement in survival and quality of life with treatments; time to clinical deterioration (including switch of drug therapy and lung transplantation); adverse events associated with treatment withdrawal; and incremental cost-effectiveness ratios (ICERs) for the interventions compared with supportive treatments.

Potentially problematic factors

- **Trials including patients with mixed functional classes:** given that none of the interventions are licensed for functional class II and only one of them (epoprostenol) is licensed for functional class IV, the main focus of the technology assessment will be on patients in functional class III. Nevertheless, existing trials may have included patients of various functional classes (for example, functional classes II-IV). Data for the specific subgroup of patients in functional class III may not be available and will need to be obtained from the sponsors/investigators of the trials.

- **Trials including patients with mixed categories of PAH:** existing trials may include PAH of very different nature (as described in section 4.1). Separate data for specific patient groups may not be available and will need to be obtained from the sponsors/investigators of the trials.

- **Insufficiency of data for subgroup analysis:** as described in section 4.1, the volume of existing evidence may not be sufficient for the exploration of treatment effects in subcategories of PAH or PAH associated with specific conditions.

- **Lack of long-term survival data from RCTs:** survival is likely to be one of the key outcomes that affect the cost effectiveness of the interventions, but it is envisaged that data from RCTs would not allow direct assessment of benefit in survival due to the short duration of the trials. Economic modelling based on comparisons involving historical controls or data from non-randomised studies

seems inevitable. Prediction of survival based on patients' risk factors and/or surrogate outcomes such as haemodynamic assessment may also be needed.

- **Rapid and continuing development of treatment algorithm and patient pathway:** different treatment guidelines have been drawn by various organisations, and are being updated rapidly. For example, we are aware that the guidelines issued by the European Society of Cardiology are being updated and new guidelines will be issued in 2008.

- **Co-morbidity and functional capacity can affect treatment choice:** for example, bosentan and sitaxentan cannot be considered in patients with moderate to severe hepatic impairment; epoprostenol cannot be considered in outpatients who are unable to closely follow the procedure to reconstitute the preparation.

Request of data from manufacturers/sponsors

A complete list of relevant randomised controlled trials sponsored by the manufacturers and reports for any unpublished trials identified within the list will be requested from individual sponsors to minimise the potential impact of publication bias.

Because of the discrepancies between the patient groups included in clinical trials and the patient groups for whom the interventions are licensed, it is expected that additional data that may not be available in the published literature will need to be obtained in order to perform analyses that is pertinent to the final scope. The data required are baseline values (where appropriate) and outcomes at latest follow-up for all the items listed under 'Outcomes' within section 5.2 below.

Areas that are considered outside the scope of the appraisal

The assessment group is aware of the emerging evidence that suggests potential benefit of early treatment in patients with PAH who have mild symptoms and functional limitation. This group of patients, however, is excluded from the final scope as none of the interventions being considered are currently licensed for PAH patients of functional class II. The availability of trial evidence in relation to this group of patients will be highlighted in the assessment report although the data will not be included in the primary analysis (see Section 5.3).

Drugs and preparations that are not currently licensed for treating PAH in the UK, such as treprostinil and iloprost intravenous infusion will not be considered as an intervention, even though they may be being used in clinical practice. However, intravenous iloprost will be considered as a comparator where evidence permits according to the final scope of the appraisal.

5. Report methods for synthesis of evidence of clinical effectiveness

A systematic review of RCTs will be conducted for the assessment of efficacy, tolerability, and safety of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for the treatment of PAH.

No systematic search of observational studies (i.e. non-RCTs) and synthesis of data from these studies are planned. If necessary, data from observational studies in relation to long-term effectiveness and safety may be described in the assessment report separately from the review of RCTs. Data from observational studies may also be used to inform parameters of economic model (see section 6).

The methods to be used for the review of RCTs are described below.

5.1 Search strategy

The following resources will be searched for relevant primary studies:

- Bibliographic databases: Cochrane Library, MEDLINE(Ovid), MEDLINE In-Process & Other Non-Indexed Citations (Ovid), EMBASE (Ovid). Searches will be based on index and text words that encompass the condition: pulmonary arterial hypertension and the interventions: epoprostenol, iloprost, bosentan, sitaxentan and sildenafil. If appropriate, a methodological 'filter' will be applied to identify trials.
- Citations of relevant studies will be examined.
- Further information will be sought from contacts with experts.
- Research registries of ongoing trials including National Research Register, Current Controlled Trials, Clinical Trials.gov
- Relevant internet resources
- Industry submissions

No specific search for conference abstracts is planned, as searches of the above resources (in particular research registries and contacts with experts and sponsors) would have allowed the identification of most, if not all, existing and ongoing trials.

The searches will not be limited by date and there will be no language restrictions. A sample search strategy for MEDLINE can be found in Appendix 2.

5.2 Inclusion and exclusion criteria

Selection of studies will be based on the following criteria. **The criteria in relation to population, interventions and comparators are purposefully broader (less specific) than those stated in section 4 (decision problem)** in order to allow the inclusion of all RCTs that can potentially contribute data relevant to the decision problems.

Study design

Only randomised controlled trials (RCTs) with duration of one week or longer will be included. Systematic reviews of RCTs will be included only for the purpose of identifying additional trials and obtaining data from RCTs that are not published elsewhere.

Population

Adults with PAH (Category 1 of Venice 2003 clinical classification) will be included.

RCTs that included patients with other forms of pulmonary hypertension (Category 2 – 5 of Venice 2003 clinical classification) in addition to PAH will be included if the data for the subgroup of patients with PAH are available. Where the patients with PAH constituted more than half of the study population but separate data for PAH are not available, the trials will be included only in sensitivity analysis.

Only patients with PAH in NYHA/WHO functional class III will be included in primary analysis (except class IV for epoprostenol). Data stratified by functional classes, if not published, will be requested from the sponsors/investigators for RCTs that included patients with mixed functional classes. Where such data are not available, the trials will be included only in sensitivity analysis.

Interventions

The following interventions will be included:

Epoprostenol, administered by continuous intravenous infusion
Iloprost, administered by inhalation through a nebuliser
Bosentan, administered orally
Sitaxentan, administered orally
Sildenafil, administered orally

No restriction on doses will be applied during the stage of study selection.

Comparators

Any treatments other than different doses, formulations or methods of administration of the intervention itself will be included. These cover placebo, conventional supportive treatments, other interventions being considered in this appraisal, other treatments not currently licensed in the UK (e.g. intravenous iloprost), and any combination of these.

Outcomes

Study selection will not be based on outcomes being measured or reported in the trials.

Based on the above inclusion/exclusion criteria, study selection will be made independently by two reviewers. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

5.3 Data extraction strategy

Data will be extracted independently by two reviewers using a standardised data extraction form. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

In addition to the information regarding study design and characteristics of study participants, the following outcomes will be sought from relevant RCTs:

- Survival
- Time to clinical deterioration (including switch of drug therapy and lung transplantation)
- Health-related quality of life
- Exercise capacity (6-minute walk test)
- Symptomatic improvement
- Frequency and duration of hospitalisation and outpatient/GP visits
- Serious adverse events
- Adverse events that are considered as clinically relevant or having potential impact on tolerability
- Withdrawal for any reasons
- Withdrawal due to lack of efficacy
- Withdrawal due to adverse events
- Haemodynamic assessment, e.g. cardiac index, right atrial pressure, pulmonary arterial oxygen saturation, pulmonary arterial pressure and pulmonary vascular resistance.

5.4 Quality assessment strategy

The quality of the individual studies will be assessed independently by two reviewers. Any disagreements will be resolved by discussion and if necessary a third reviewer will be consulted. The quality of the clinical effectiveness studies will be assessed according to criteria based on NHS CRD Report No.46.

5.5 Methods of analysis/synthesis

Primary analysis

Where evidence permits, meta-analysis will be carried out separately for each of the interventions being considered for the outcomes specified above. The primary analysis will include data for licensed doses only (where appropriate) for patients with pulmonary arterial hypertension (all subcategories in Category 1 of the Venice 2003 clinical classification excluding the subcategory 1.5 persistent pulmonary hypertension of the newborn) in NYHA/WHO functional class III (and functional class IV for epoprostenol) using the latest follow-up data available from the randomised, controlled period of each trial. A random effects model will be used given the heterogeneous population within PAH. Comparisons to be made include each of the interventions versus placebo (with ongoing supportive treatments); each of

the interventions versus supportive treatment (if trials available); comparison of the interventions against each other (if trials available); and comparison between different combinations of interventions (if trials available). No indirect comparison or mixed treatment comparison is planned.

Subgroups to be examined

Where evidence permits, subgroup analysis will be carried out on a few key patient populations defined by subcategory of PAH/underlying disease condition and/or functional class. The selection of subgroups to be examined has been described in section 4.2. Appropriate comparisons relevant to the specific patient populations will then be carried out.

Assessment of heterogeneity

Statistical heterogeneity between studies will be assessed by χ^2 test and I^2.

Assessment of publication bias

All manufacturers will be requested to provide a list of all company-sponsored RCTs that are relevant to this appraisal. Requests will also be made for reports of unpublished trials and data that are potentially available but not reported in published papers. Where there is sufficient number of RCTs, publication bias will be assessed using Begg's rank correlation test and Egger's linear regression test.

Sensitivity analysis

Where the evidence permits, sensitivity analyses will be carried out to explore factors, chosen among the following, that may be influential to study outcomes

- Quality measures of RCTs such as blinding.
- Factors associated with the characteristics of the study population, such as the mix of functional classes or subcategories of PAH.
- Factors associated with study design such as study duration and drug doses.
- Exclusion of data supplied as commercial in confidence.

6. Report methods for synthesising evidence of cost-effectiveness

A comprehensive search for literature on the cost and cost-effectiveness of drugs for PAH will be carried out.

Studies on costs, quality of life, cost effectiveness and modelling will be identified from the following sources:

- Bibliographic databases: MEDLINE (Ovid), EMBASE (Ovid), CINAHL (Ovid), Cochrane Library (Wiley) DARE and NHS EED and the Office of Health Economics HEED database.

- Industry submissions
- Internet sites of national economic units

Searches will not be limited by date and there will be no language restrictions.

Standard approaches to applying inclusion/ exclusion criteria will be employed. Quality assessment for cost-effectiveness studies will be done using standard criteria.[1,2] Papers may be excluded at this stage on the basis of quality assessment. Justification for the exclusion of papers will be presented. The papers that remain in the review will be summarised on the basis of key items of information, an example of which is listed below.

- Details of the study characteristics such as form of economic analysis, comparators, perspective, time horizon and modelling used.
- Details of the effectiveness and cost parameters such as: effectiveness data; health state valuations; resource use data; unit cost data; price year; discounting assumptions; productivity costs.
- Details of the results and sensitivity analysis.

Searches for additional information regarding model parameters, patient preferences and other topics not covered within the clinical effectiveness and cost-effectiveness reviews will be based on the methodological discussion paper produced by InterTASC (January 2005).

6.1 Economic Evaluation

As described in section 4 (decision problem), PAH covers diverse patient populations and disease severity. Given the expected paucity of evidence for many of the patient populations and the constraint of resources for this technology assessment, the cost-effectiveness of the interventions being considered will be explored in a key patient population identified as most relevant to the interventions and having the most robust evidence according to the clinical effectiveness review.

Where feasible and sensible the economic analysis will conform to the NICE reference case. Any major deviation from the reference case will, however, be discussed with colleagues at NICE before being implemented.

A model-based economic evaluation will be conducted as part of this appraisal. The structure of the model will be considered in light of the existing published models in this clinical area (e.g. see Highland et al 2003[3] and Wlodarczyk et al 2005[4]) and will be developed in collaboration with clinical experts. The choice of model type has to be guided by the nature of the clinical condition and is likely to be either a decision tree or a Markov model.

The perspective for the base-case cost analysis will be the NHS and Personal Social Services. The analysis will be conducted with a number of different time horizons (including both short-term, such as 1 year, and longer-term, such as 10 years), given the high levels of uncertainty that will inevitably be associated with long-term horizons in this clinical area. Longer-term analyses will be discounted in line with

reference case recommendations and so a rate of 3.5% will be applied to both costs and benefits.

It is our intention for this economic analysis to express effectiveness in terms of quality-adjusted life years (QALYs). It is, however, possible that standard utility-based measures of health related quality of life, such as the EuroQol EQ-5D, have not been used widely in this clinical area. Thus, whilst our intention is to conduct a cost-utility analysis, with QALYs as the measure of outcome, data limitations may be considerable and if this proves to be the case then the analysis will be of a cost-effectiveness format with effects expressed in more natural clinical units such as life years gained.

The uncertainties in this analysis will be considerable and so extensive sensitivity analyses will be undertaken. These will take the form of both conventional one and multi-way analyses (where the values of key input parameters are varied) and probabilistic sensitivity analysis (PSA). The use of PSA will involve specifying distributions around model parameters (such as probabilities, costs, utilities, etc.) and sampling from such distributions. This analysis will then allow results to be presented as scatter plots on the CE plane and as cost-effectiveness acceptability curves.

7. Handling the company submissions

Company submissions by the manufacturers/sponsors will be considered if received by the TAR team no later than 10 May 2007. Company submission material of any nature arriving after this date will not be considered.

If the clinical information meets the inclusion criteria for the review it will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model.

Any 'commercial in confidence' data taken from a company submission will be underlined and highlighted in the assessment report (followed by an indication of the relevant company name e.g. in brackets).

8. Competing interests of authors

None (except clinical advisors – to be confirmed).

9. Appendices

Appendix 1 Background

Pulmonary arterial hypertension (PAH) is a diverse group of diseases characterised by a progressive increase of pulmonary vascular resistance, which leads to right ventricular failure and premature death if untreated. It is defined by a mean pulmonary artery pressure greater than 25 mmHg at rest or greater than 30 mmHg with exercise.[5] Symptoms of PAH include dyspnoea, fatigue, chest pain, syncope, and oedema.

Classifications

PAH can be classified according to clinical or pathological features. In addition, patients with PAH are classified according to their functional capacity. The following paragraphs described clinical classification and functional classification of PAH that are referred to throughout this protocol.

Clinical classification

Pulmonary hypertension was traditionally classified into two categories: primary pulmonary hypertension or secondary pulmonary hypertension depending on the absence or presence of identifiable causes or risk factors. In 1998, the World Health Organisation (WHO) co-sponsored a symposium on pulmonary hypertension which took place in Evian, France. A new clinical classification of pulmonary hypertension based on pathophysiological mechanism, clinical presentation and therapeutic options was proposed in the symposium. This 'Evian classification' (or sometimes referred to as WHO 1998 classification) includes five major categories, with pulmonary arterial hypertension being one of the categories. The term 'primary pulmonary hypertension' was retained within this category and included subcategories of 'sporadic PAH' and 'familial PAH'. It was agreed that the term 'secondary pulmonary hypertension' should be abandoned. In a subsequent symposium that took place in Venice, Italy 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'. The details of Venice 2003 clinical classification are listed in Table 1.[5]

Functional classification

Traditionally, patients with PAH are classified according to the classification of functional capacity developed by the New York Heart Association (NYHA) for patients with cardiac diseases based on clinical severity and prognosis. An adaptation of the NYHA functional classification specifically for patients with pulmonary hypertension was proposed in the aforementioned WHO symposium in Evian. The WHO classification and NYHA classification are nearly identical and are sometimes referred to as NYHA/WHO classification, which is listed in Table 2.[5]

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
        - 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)

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.

References

1 Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. BMJ 1996;313:275-83.

2 Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: consensus on health economic criteria. International Journal of Technology Assessment in Health Care 2005;21:240-5.

3 Highland KB, Strange C, Mazur J, Simpson KN. Treatment for pulmonary hypertension: a preliminary decision analysis. Chest 2003;124:2087-92.

4 Wlodarczyk JH, Cleland LG, Keogh AM, McNeil KD, Perl K, Weintraub RG, *et al*. Public funding of bosentan for the treatment of pulmonary artery hypertension in Australia: cost effectiveness and risk sharing. Pharmacoeconomics 2006;24:903-15.

5 Galiè N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, *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.

Appendix 2: sample search strategy for MEDLINE

Database: Ovid MEDLINE

1 hypertension pulmonary/ (15879)
2 pah.mp. (6246)
3 pulmonary hypertension.mp. (15684)
4 pulmonary arterial hypertension.mp. (1584)
5 pulmonary artery hypertension.mp. (454)
6 or/1-5 (27610)
7 (epoprostenol or flolan or prostacyclin).mp. (15388)
8 (iloprost or ventavis).mp. (1802)
9 (bosentan or tracleer).mp. (996)
10 (sitaxentan or thelin).mp. (7)
11 (sildenafil or revatio).mp. (2672)
12 or/7-11 (19451)
13 6 and 12 (1558)
14 randomized controlled trial.pt. (227224)
15 controlled clinical trial.pt. (73803)
16 randomized controlled trials.sh. (46105)
17 random allocation.sh. (56575)
18 double blind method.sh. (88793)
19 single blind method.sh. (10465)
20 or/14-19 (385746)
21 (animals not human).sh. (3961394)
22 20 not 21 (353883)
23 clinical trial.pt. (430669)
24 exp clinical trials/ (184870)
25 (clin$ adj25 trial$).ti,ab. (124137)
26 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (87999)
27 placebo$.ti,ab. (98836)
28 random$.ti,ab. (355652)
29 placebos.sh. (25653)
30 research design.sh. (45569)
31 or/23-30 (816422)
32 31 not 21 (717894)
33 32 not 22 (379251)
34 comparative study.sh. (0)
35 exp evaluation studies/ (577290)
36 follow up studies.sh. (329331)
37 prospective studies.sh. (213191)
38 (control$ or prospectiv$ or volunteer$).ti,ab. (1714646)
39 or/34-38 (2481774)
40 39 not 21 (1831076)
41 39 not (22 or 33) (2033544)
42 22 or 33 or 41 (2766678)
43 13 and 42 (597)