National Institute for Health and Clinical Excellence

Drugs for the treatment of pulmonary arterial hypertension

Comments on the draft scope: second consultation October 2006

Section	Consultees	Comments	Action
Background information	Actelion Pharmaceuticals UK Ltd	a)Para One : In order to highlight the severity of the disease, the background section should include reference to the significant mortality associated with untreated PAH. The average survival time for adult patients and paediatric patients with severe disease is less than 2.5 yrs and 10 months respectively.(D'Alonzo et al, 1991).	Added median survival in severe disease – 2.8 years without specific treatment – taken from ESC guideline (2004) (based on D'Alonzo)
		b) Para Six: Patients with PAH may have thrombosis as a contributory factor. Patients in whom it is a major factor, and who therefore may be treated via pulmonary thromboendartarectomy (PTCA), are not classed as PAH, but fall within Class IV of the 2003 classification. Reference to PTCA as a treatment should therefore be removed from this paragraph.	Deleted paragraph
		c) Para Three: The following sentence is innacurate:'All drugs are likely to be licensed for the treatment of PAH'. and should be corrected to ' These therapies will be licensed for one or more sub-groups of PAH'. As described in the 'Technologies' section, the prostaglandins are only licensed for a subgroup of PAH, primary pulmonary hypertension.	Deleted sentence – updated technology section with further details of licensing
		d) Para five: prevalence data for the potential treatment population should be inserted. Data from published literature give estimates for severe patients, ie those in WHO functional classes III and IV, who may require treatment with the therapies under review, are 30 - 30/million (ref Peacock, BMJ, 2003)	Add prevalence figures from reference cited

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	British Cardiovascular Society (comments also endorsed by the Royal College of Physicians)	Para 1: The definition of pulmonary arterial hypertension (PAH) includes not only the stated pulmonary arterial pressures but also "a pulmonary capillary wedge pressure </= to 15 mm Hg and a pulmonary vascular resistance >/= 3 Wood units or 240 dynes/sec/cm5.	Definition taken from ESC guideline 2004 (does not mention pulmonary capillary wedge pressure in the definition)
		Para 2 and 3: It would be better to describe the Venice clinical classification as having 5 categories rather than classes, since the latter term is used to describe symptom severity (NYHA functional classes I - IV). Note that not all drugs are licensed for PAH (see comments below).	Amended reference to classes for clinical classification Added reference to functional classification.
Background information (continued)	British Cardiovascular Society (continued)	Para 5: this is the incidence of idiopathic PAH. Incidence and prevalence of PAH in other diseases included in PAH is less clear. For pragmatic reasons it may be better to consider the number of patients currently treated by these technologies in NSCAG / NSD designated centres in the UK. Based on census data collected on 31st March each year since 2004, the number of patients on the listed interventions either paid by the NHS or clinical trials was 638 in 2004, 912 in 2005 and 1242 in 2006.	The licensed indications for the drugs under consideration include only primary PAH (familial and idiopathic) and in some cased PAH associated with connective tissue disease. NSCAG figures may include others. Figures derived from BMJ paper 2003, by Peacock.
		Para 6 (page 2): The aims of treatment should include reversal of pulmonary vascular remodelling. In addition to improving symptoms, the aim of treatment is to improve exercise capacity and survival.	Added improve exercise capacity and prolong survival.
		Reference to thromboembolic pulmonary hypertension and pulmonary endarterectomy surgery should be removed since this belongs to category 4 of the Venice clinical classification and not PAH.	Removed reference to pulmonary endarterectomy
		See separate comments about calcium channel blockers below under comparators. "Symptomatic treatments" should be referred to as "supportive treatments".	Amended comparators

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Background information (continued)	Encysive (UK) Ltd	1: The background information says little about the seriousness of PAH and its impact on patients' lives and outcomes. Pulmonary arterial hypertension is a serious and progressive disease affecting the pulmonary vascular endothelium of the small pulmonary vessels that ultimately leads to right ventricular failure and death. For patients it is characterised by a gradual and progressive onset of shortness of breath, fatigue, angina pectoris, fainting or syncope, and peripheral oedema which becomes seriously disabling and ultimately fatal. A survey by PAH-UK in 2002 found that "over 50% of patients felt that their condiction impacted significantly on their ability to shop, to work, to socialise and to go on holiday. Over 60% of patients said that their condition has significantly affected their life financially, mainly by having to give up work." (Impact Survey 2002, at www.pha-uk.com/research.asp#) In 1980 the National Institutes for Health (NIH) established a registry on Primary Pulmonary Hypertension that described the clinical characteristics of the disease and its natural history over a 5-year period. The median survival was 2.8 years, with survival rates of 68%, 48% and 34% at 1, 3 and 5 years respectively (Rich S, Dantzker R, Ayres S et al. Ann Intern Med 1987; 107; 216-223). A subsequent study, following introduction of Flolan, observed survival at 1 and 3 years as 87.8% and 62.8%, significant improvements ($p<0.001$) (Mclauchlin V, Shillington A, Rich, S. Circulation 2002;106: 1477-1482).	Added reference to median survival
		2. The background information makes no reference to WHO functional class. This classification of disease severity is critical to evidence-based treatment protocols, and underlies the key treatment guidelines, the European Society of Cardiology evidence-based treatment algorithm for PAH (European Heart Journal 2004, 25, 2243-2278). In those guidelines, and in clinical practice, symptomatic treatments (calcium channel blockers, anticoagulants, digoxin and diuretics, alone or in combination) are recommended as general measures and background therapy following diagnosis, but for patients in Functional Class III active intervention using prostacyclin and prostacyclin analogues, endothelin-1 receptor antagonists or phosphodiesterase-V inhibitors is additionally recommended.	Added WHO/NYHA functional classification
		3. No comments on incidence/prevalence.	

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Background information (continued)	Encysive (UK) Ltd (continued)	4. The aims of treatment should make specific reference to safety, and the use of treatments with the most favourable risk/benefit ratio; sustainability, and the use of treatments which can continue to be used throughout therapy; and most importantly to improved survival.	The appraisal will cover clinical and cost effectiveness of these agents. Safety and risk/benefit is the remit of the regulatory authorities.
	GlaxoSmithKline	We suggest that paragraph 3 of this section which describes the divisions of the WHO groups should precede paragraph 2 which then describes the sub-categories under these divisions.	Amended
		For completeness, this section should include definitions according to the NYHA classification. Additional information about the disease would also help to clarify the disease area. We suggest inclusion of prevalence data, age range of patients and the relative differences in diagnoses and prognoses between the classes i.e. patients in Class I and Class II are not easy to diagnose and have a better prognosis compared with patients in Class IV.	Add WHO/NYHA functional classification
		With regard to the revision of the clinical classification of pulmonary hypertension (2003) we suggest that patients are categorised in 'groups' rather than in 'classes'. Classes should be limited to divisions based on functional capability.	Amended
		In paragraph 6 of this section it should be noted that this disease is associated with high mortality. We suggest that the aims of treatment are to reduce progression of disease and to increase patient survival.	Amended
		Calcium channel blockers are reserved for the small sub-group of patients who respond positively to NO or other vasodilator testing. Such patients are not considered to be typical PAH patients. We would suggest therefore that calcium channel blockers cannot be considered as standard comparator therapy. Similarly anti-coagulants, digoxin or oxygen are not standard treatment or comparators. We suggest that these drugs are more appropriately described as usual background therapy because the reasons for use are not related to the primary goals of treatment.	Amended as follows “Some patients with idiopathic PAH respond to calcium channel blockers.” Population in scope also amended (see below).

Section	Consultees	Comments	Action
Background information (continued)	Pulmonary Hypertension Association UK	The mention of CCBs needs to viewed only in relation to the very small patient population that the clinical evidence can identify to help. Its specific mention here seems very much out of place.	Amended
	Raynaud's & Scleroderma Association	It should be pointed out that not all types of PAH have the same outcome and that scleroderma associated PAH is especially severe with higher mortality than other types	Scope updated to reflect higher mortality with connective tissue disease
	Royal College of Nursing	Scope seems fine and there are no further comments to be submitted on behalf of the Royal College of Nursing.	Noted
	Dr Harbinson on behalf of Department of Health, Social Service & Public Safety, Northern Ireland (DHSSPSNI)	Accurate but brief. There are difficulties about the subtypes of pulmonary hypertension as the new classification was not used in the inclusion criteria of some of the studies.	Noted
	Prof Nicholls on behalf of DHSSPSNI	Good	Noted
The technology/ intervention	Actelion Pharmaceuticals UK Ltd	Epoprostenol, an IV prostaglandin, should be removed from the list of interventions and moved to the list of comparators. In 2001, specialist PAH centres were designated by NSCAG, largely in order to provide the infrastructure and support to manage the administration of prostaglandins more effectively and safely. PGs have been used in this patient population since the 1990s and are thus part of the 'standard of care'.	Comparisons will be made between the technologies listed, therefore the comparison with prostaglandins will be made.

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	British Cardiovascular Society (comments endorsed by the Royal College of Physicians)	Calcium channel blockers should be considered an intervention and not a comparator. Calcium channel blockers are an intervention for a small group of patients with idiopathic or familial PAH(<10%) who have a positive vasodilator response at cardiac catheterisation. In such patients, about half will have a satisfactory long-term response to these drugs without the need for the other interventions being assessed. Those patients who fail calcium channel blocker therapy will require treatment with one of the other interventions being assessed. Calcium channel blockers do not have any role in any other PAH patients. Although beraprost has been used in trials in PAH it is not available in the UK.	Unlicensed treatments cannot be considered as interventions in a technology appraisal – no change to scope. The population will be those for whom calcium channel blockers are unsuitable as per the algorithm suggested in the ESC guideline (2004). Beraprost will not be included.
The technology/ intervention (continued)	Encysive (UK) Ltd	The description of Thelin (sitaxentan) is consistent with the European marketing authorisation. Iloprost (Ventavis) is marketed by Schering Health Care Ltd, not Schering-Plough.	Amended
	GlaxoSmithKline	For accuracy, the description in the first paragraph under this section should be amended as follows: Prostacyclin is a naturally occurring prostaglandin. Epoprostenol is a synthetic prostacyclin.	Amended
	Pfizer Ltd	Under bosentan the following comment should be included: "Efficacy has been shown in PAH and PAH secondary to scleroderma with no significant interstitial pulmonary disease".	Amended as per summary of product characteristics.
	Pulmonary Hypertension Association UK	We wish to ensure that Flolan is viewed within the whole process of this appraisal as the 'standard of care' or as is termed in this draft document as conventional therapy. Also, while the use of Iloprost IV is not licensed, it needs to be understood that it is more commonly used than Flolan IV in the UK and has been for many years.	The comparison with epoprostenol will be made because all of the interventios may also be considered comparators. Iloprost will be included as a comparator
	Raynaud's & Scleroderma Association	Clarification of the drugs licensed for scleroderma PAH should be provided	Updated to include licensed indications in more detail.

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	Schering Health Care Ltd	Please note the manufacturer of iloprost (Ventavis) is Schering Health Care and not Schering Plough.	Amended
	Dr Harbinson on behalf of DHSSPSNI	Yes *[In answer to the question "is the description of the technology or technologies accurate?]*	Noted
	Prof Nicholls on behalf of DHSSPSNI	Yes *[In answer to the question "is the description of the technology or technologies accurate?]*	Noted
Population	Actelion Pharmaceuticals UK Ltd	In order to reflect the population for whom the treatments being assessed are approved, the population should be further limited to a sub-group of Venice Group I patients, ie the more severe patients, in WHO functional classes III and IV. All therapies should be assessed only at their approved doses.	Added, but note that epoprostenol is the only drug licensed for functional class IV
	British Cardiovascular Society (comments endorsed by the Royal College of Physicians)	Not all drugs are licensed for the whole pulmonary arterial hypertension group of diseases. Most are licensed for only idiopathic and familial PAH (which together were previously described as primary pulmonary hypertension). Even when drugs are licensed for the whole group, trial data has not been collected for all diseases. This is usually because the numbers of affected patients are small although the interventions being assessed may be life-saving in these patients. No drugs are licensed for children.	Licensed indications have been updated in background section.
	Encysive (UK) Ltd	The definition proposed (Class 1 of the revised Venice classification of pulmonary hypertension) is appropriate, except that it excludes pulmonary hypertension due to chronic thrombotic and/or embolic disease (Venice class 4). For these patients the diagnosis, pattern of disease progression and treatment are similar to Class 1 patients, and they should therefore be included within the scope of the appraisal.	None of the drugs is licensed for pulmonary hypertension due to chronic thrombotic and/or embolic disease (Venice class 4).
	GlaxoSmithKline	It should be noted that whilst none of the treatments have a specific licence in the group, they are all used in paediatrics.	Noted – but children will not be included for this reason.

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	Pfizer Ltd	Restricting the population to those under Class I of the Venice classification list is appropriate.	Noted
	Raynaud's & Scleroderma Association	It is sensible to point out that half the cases of PAH are caused by associated conditions and that outcomes may be different in these groups	Added note about subgroups to the 'other considerations' section
	West Midlands Health Technology Assessment Collaboration	Should children and adults be considered separately?	None of the drugs is specifically licensed for children, therefore children will not be considered in the appraisal.
Population (continued)	Dr Harbinson on behalf of DHSSPSNI	There have been some data on using these agents in other patients than the class I PAH population e.g. patients with Eisenmenger's syndrome. The committee may find this use too specialised to make specific comment.	Only licensed indications will be considered.

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Comparators	Actelion Pharmaceuticals UK Ltd	a) As discussed and agreed at the original scoping meeting, calcium channel blockers (CCBs) are not a relevant comparator. There is extensive evidence demonstrating that only a minority of patients (<7%) respond, and it is hypothesised that they have a slightly different disease. (Sitbon et al, 2005) b) From the 1990s until 2002, 'standard of care' for WHO class III and IV patients has included diuretics/warfarin/oxygen (palliative care), PLUS prostaglandins (PGs). See refs below. Actelion propose that the Scope should be ammended to reflect this fact. i) Barst et al, 1999 - describes clear improvement in mortality in children administered prostacyclin from 1987, compared to children without this option pre-1987. ii) Williams et al, 2006 - describes the comparison between a historic, control group, pre-2002 of whom 57% received PGs, versus a current treatment group. iii) Rubin et al, 2002- describes the pivotal, 16 week, RCT of bosentan. By week 16, 4% of patients in the comparator, palliative care group, were already receiving PGs while 7 % had discontinued palliative care and moved to another therapy (details not known). This controlled study was limited to 16 weeks due to ethical concerns about continuing palliative care any longer. iv) UK Heart Guidelines (S Gibbs et al, 2001) - state that severe patients should be considered for treatment with PGs. Since 2002, 'standard treatment' has also included others in the list of interventions being assessed. (ref European Society of cardiology , 2004). Actelion believe that, since the focus in today's NHS is on patient centred care, it is not acceptable practise to offer palliative care to this group of severely ill patients as 'standard care'.	Calcium channel blockers will not be considered as comparators and the population to be considered has also been amended. Comparisons with prostaglandins will be covered in addition to comparisons with supportive care.

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Comparators (continued)	British Cardiovascular Society (comments endorsed by the Royal College of Physicians)	Intravenous epoprostenol is considered the gold standard against which other interventions should be compared. It was the first intervention for which there was randomised trial evidence (1996) and became the standard therapy for all NYHA functional class III and IV patients in Europe and the USA in the 1990s.	Comparisons with prostaglandins will be covered in addition to comparisons with supportive care.
		Heart-lung or double lung transplantation is a further suitable comparator since pulmonary hypertension does not recur post-operatively. Owing to the limited availability of donor organs fewer than 10 patients per annum with PAH undergo transplantation in the UK.	Transplantation is not included as a comparator (but included under outcomes) given the limitations on availability.
		Diuretics, warfarin and oxygen are considered supportive therapy. There are no studies of diuretics in PAH. Warfarin has circumstantial evidence for improved survival from two observational studies in idiopathic and familial (primary) PAH.	Diuretics, warfarin and oxygen are now described as supportive treatments.
		Data for oxygen are circumstantial. Although recommended for idiopathic and familial PAH in guidelines it is generally agreed that more data is required to determine how it affects the natural history of the disease.	
		Calcium channel blockers should not be considered as a comparator. Rather calcium channel blockers are an intervention (see comments in technologies section).	Calcium channel blockers are not licensed for PAH.
	Encysive (UK) Ltd	The “standard treatments” listed in the draft scope (calcium channel blockers, diuretics, warfarin and oxygen therapy) are recommended in the ESC guidelines as general measures and background therapy following diagnosis. They are not indicated for the treatment of PAH, and are not appropriate for the treatment of all PAH patients. They should be regarded as palliative therapy. For PAH in patients in Functional Class III active intervention using prostacyclin and prostacyclin analogues, endothelin-1 receptor antagonists or phosphodiesterase-V inhibitors is recommended. The “standard treatments” should be considered as background therapy for the technologies subject to this appraisal, and not as comparators.	Calcium channel blockers will not be considered as comparators and the population to be considered has also been amended. Comparisons with prostaglandins will be covered in addition to comparisons with supportive care.
	GlaxoSmithKline	Please see note on background therapy in section on 'Background information'.	See above

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Comparators (continued)	Pfizer Ltd	No (also see comment above re:population). The therapies listed in the draft scope can not be considered standard comparators. CCBs are only appropriate for those patients who have a positive adenosine test (approximately 10%) (1.Humbert M, et al. Treatment of Pulmonary Hypertension NEJM 2004 351:1425-1436. 2. 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. (link provided in covering E-mail as your formatting does not permit inclusion here.). Diuretics are useful in patients with right heart failure. In the clinical trials of epoprostenol, sildenafil, bosentan and iloprost 47 to 70% of paitents were on diuretics. Warfarin is given as an anti-coagulant to avoid thrombo-embolic complications. It is the expectation that by the time patients achieve Functional Class III (usually at diagnosis) that they will require oxygen therapy for symptom relief. The licensed therapies described as the technology/intervention in this scope are the comparators that should be identified for patients with PAH. For patients with PAH Functional Class III the comparator is each of the other licensed therapies. The expectation would therefore be (where data exists) for a pairwise comparison of all therapies licensed for symptom relief in patients with severe PAH at the time of the appraisal. In the absence of head to head data an adjusted indirect comparison using an approach that preserves the random allocation of the original trials should be considered. Pfizer is aware that combinations of sildenaifil, and/or bosentan and/or epoprostenol/iloprost have been used in clinical practice. Pfizer is unaware of any such combination being recomended as an appropriate regimen within a product label or a clnical guideline.	Calcium channel blockers will not be considered as comparators and the population to be considered has also been amended. Comparisons with prostaglandins will be covered in addition to comparisons with supportive care. Combination therapy will be considered if the evidence allows.

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Comparators (continued)	Pulmonary Hypertension Association UK	CCBs are of little use in over 90% of PH patients, in no way can they be used as a standard treatement in this disease. The only standard comparator that can be used (based on clinical evidence) is Flolan. Flolan has been the standard default treatemnt for patients involved in clinical trails over the years when patients experience deterioration.	Comparators and background information updated as described above.
	Raynaud's & Scleroderma Association	Calcium channel blockers are of almost no use in scleroderma associated PAH and cannot be regarded as standard therapy for comparison	Calcium channel blockers removed as comparators.
	Prof Nicholls on behalf of DHSSPSNI	Yes. About 10-20% respond to a calcium channel blocker, the rest don't, and other agents used in systemic hypertension (e.g. beta-blockers, ACE inhibitors etc) may be hazardous. Diuretics just keep the leg swelling down. Warfarin has little value unless there is a background of thromboembolism, and again can be hazardous. Oxygen provides temporary relief and may reduce PA pressure. The main problem has been the lack of knowledge about the physiology of the pulmonary circulation, and especially the role of prostaglandins and endothelin. The development of specific drugs/new technologies has revolutionised our approach to this condition.	Calcium channel blockers removed as comparators. Other treatments defined as supportive therapy.
Outcomes	Actelion Pharmaceuticals UK Ltd	The outcomes listed within the scope would benefit from being identified as those which are regarded either as: a)The primary outcome and b) As secondary outcomes. Survival benefit should be clearly identified as the single primary outcome , with all others listed as secondary. It should be noted that the secondary outcome of improvement in exercise capacity, measured via the 6 minute walk test, is a surrogate, and is not predictive of mortality benefits.	Not appropriate for scope, no action required for scope. See reference case.

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Outcomes (continued)	British Cardiovascular Society (comments endorsed by RCP)	The outcome measures are appropriate	Noted
	Encysive (UK) Ltd	The proposed outcome measures are appropriate, except that "time to clinical deterioration" should be defined in a way which also includes switch to or addition of an alternative pharmacological therapy.	Amended time to clinical deterioration outcome as recommended.
	GlaxoSmithKline	As far as we are aware *[in answer to the question "Will these outcome measures capture the most important health related benefits of the technology?"]*	No action required
	Pfizer Ltd	Yes *[in answer to the question "Will these outcome measures capture the most important health related benefits of the technology?"]*	No action required
	Raynaud's & Scleroderma Association	Survival and breathlessness are of most relevance in connective tissue disease	No action required
	Prof Nicholls on behalf of DHSSPSNI	Good. Exercise capacity is better quantified by formal cardiopulmonary exercise testing than by a 6 minute walk, but not all centres have the capacity to do this test reliably.	No action required
Economic analysis	Encysive (UK) Ltd	Incremental cost per QALY is an appropriate measure, providing the right comparators are selected. Analysis should be conducted according to WHO functional class (see above), and should compare PAH-specific treatments. An NHS and personal social services perspective is appropriate for costing, but account should also be taken of broader economic issues: PAH occurs predominantly in a working age population.	Most drugs are only licensed for WHO functional class 3 See reference case

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Economic analysis (continued)	GlaxoSmithKline	[commericial in confidence information removed] Clarity is required on the NICE stance about whether ultra orphan status drugs are judged on a different cost effectiveness criteria compared with those generally employed in decision-making, as per the discussion paper 'Appraising Orphan Drugs' on the NICE website.	Not relevant to scope – for consideration by the appraisal committee.
	Pfizer Ltd	Pfizer agrees that the appropriate time horizon needs to reflect the prognosis associated with the diagnosis of PAH. A one year time horizon may be the most appropriate.	No action required
	Pulmonary Hypertension Association UK	In rare diseases and expensive therapies, standard outcome assessments of economic benefit are not appropriate - these need special consideration as orphan diseases	No action required
	Raynaud's & Scleroderma Association	In rare diseases and expensive therapies, standard outcome assessments of economic benefit are not appropriate - these need special consideration as orphan diseases	No action required
	Prof Nicholls on behalf of DHSSPSNI	The prognosis of IPAH is so poor that any major benefit should be readily apparent within a year.	No action required
Other considerations	Actelion Pharmaceuticals UK Ltd	In this severly ill population, treatment algorithms, or protocols, are normal practise, rather than single monotherapies. A significant proportion of patients thus move from the first line therapy to an alternative or, in some cases, to a combination. This algorithm based approach is supported by all a review of the first year of therapy in all the recent pivotal trials for the interventions being assessed. As such, treatment algorithms, rather than individual therapies, should be assessed within this appriasal.	For consideration by the assessment group in developing their protocol.

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Other considerations (continued)	British Cardiovascular Society (comments endorsed by the Royal College of Physicians)	None of the interventions being considered are curative, and in many patients PAH breaks through drug monotherapy. For this reason combination therapy is increasingly used to treat progressive clinical deterioration. Prescription of the interventions being assessed (with the exception of calcium channel blockers) is limited currently and for the foreseeable future by the Department of Health only to the seven NSCAG-designated pulmonary hypertension centres in England.	Combination therapy will be considered only if the evidence allows.
	Encysive (UK) Ltd	The scope notes that "regimens containing any of the drugs listed under interventions, either alone or in combination, may be compared to each other". None of these drugs is currently licensed for combination therapy. However, clinical practice may be tending towards combination therapy in some circumstances, and clinical trials of combination use are ongoing or planned. The scope should address this explicitly, even where it is not in accordance with (current) marketing authorisations.	Technology appraisals can only consider drugs within their licensed indications. It is unclear whether combination therapy is excluded by the current summaries of product characteristics.
	GlaxoSmithKline	Commercial in confidence information removed	
	Pulmonary Hypertension Association UK	The PHA wish to see that the place and role of the designated centers in the overall management and use of therapies is central to the considerations within this appraisal.	This is outside the scope of a technology appraisal.
	West Midlands Health Technology Assessment Collaboration	The point in the appraisal process at which a decision on whether the two technologies currently unlicensed in the UK are to be excluded or included should be defined. This should be no later than the deadline for submission of the draft protocol by the TAR team.	Unlicensed technologies have been removed from the scope.
	Dr Harbinson on behalf of DHSSPSNI	Perhaps a brief comment on the appropriate use of investigation techniques and strategies, and the use of screening for PAH in at risk populations might be helpful.	This is outside the scope of a technology appraisal.
	Prof Nicholls on behalf of DHSSPSNI	No others needed *[In answer to a request for "Suggestions for additional issues to be covered…"]*	Noted

Section	Consultees	Comments	Action
Additional comments on the draft scope	British Cardiovascular Society (comments endorsed by the Royal College of Physicians)	Comment about inclusion of children: The stated NICE objective is to appraise the clinical and cost effectiveness of treatment for Pulmonary Arterial Hypertension within their licensed indications. None of the interventions (drugs) is licensed for use in children. The Department of Health directive is that the drugs should only be prescribed by the UK Pulmonary Hypertension Service for Children, an NSCAG-designated National Clinical Network with the hub at Great Ormond Street Hospital for Children. From April 2007 the service will be NSCAG-funded, not just designated. An indirect and undesirable consequence of NICE approval of the use of PAH drugs in children would be more widespread prescribing and delay in referral to the NSCAG centre until the patient showed marked deterioration. Time from diagnosis to death in the untreated child with IPAH is only 10 months, significantly less than in adults. Also, PAH is more common in children and has more varied and complex aetiologies (excluding the Eisenmenger Syndrome) in addition to IPAH. In summary, NSCAG controls the prescribing of these unlicensed PAH drugs in children.	Given that the technologies are not specifically licensed for children, this technology appraisal will not be included in this appraisal and the scope has been amended accordingly.
	Dr Harbinson on behalf of DHSSPSNI	Other agents-I believe there are small trials on nitric oxide and L-arginine. These may be too small to merit detailed assessment. The other treatment currently offered under some circumstances is balloon atrial septostomy.	Technology appraisals can only consider drugs within their licensed indications.
	Welsh Assembly Government	There are key issues related to combination therapy and to cost effectiveness as well as a need for shared care in Wales via an MDT in S Wales linked to Cardiff & Swansea.	Combination therapy will be considered if the evidence allows.

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Additional comments on the draft scope (continued)	West Midlands Health Technology Assessment Collaboration	This scope seems to have been expanded considerably through the scoping workshop. The resulting large, complex proposed Health Technology Appraisal appears to be attempting to assess all newer medical technologies for PAH either as monotherapy, combination therapy and adjunct to standard therapy compared to standard therapy and any other regimens containing the drugs under investigation. The technologies included in the scope do not represent a single class but comprise at least 3 classes of technology each acting in a separate way. As well as comparison to other technologies, comparison within class (where possible), between class and between individiual technologies is implied by the scope. Furthermore the assessment is covering the application of the technolgies in both adults and children. Taken together this is a considerable undertaking. Given the wide aims of the scope and that it appears to be for an appraisal on which is the best /better (medical) regimens in PA, this topic may be better addressed by a guideline rather than a technology appraisal.	This is a multiple technology appraisal. The appraisals team are aware of the complexity of this condition.

The following consultees/commentators indicated that they had no comments on the draft scope

British Heart Foundation
British Hypertension Society (request to be removed from list)
Department of Health
Heart UK (request to be removed from list)
The Scleroderma Society