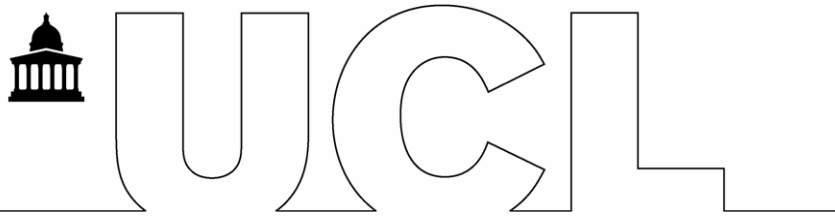
ROYAL FREE AND UNIVERSITY COLLEGE MEDICAL SCHOOL
UCL DIVISION OF MEDICINE
CENTRE FOR RHEUMATOLOGY AND CONNECTIVE TISSUE DISEASES

[redacted]

Tel:
Fax:
Email:



National Institute of Clinical Excellence (NICE)
MidCity Place
71 High Holborn
London
WC1V 6NA

7th May 2007

Dear Sirs

Please find enclosed my submission for the appraisal of Drugs for the treatment of pulmonary arterial hypertension, as the nominated expert from the British Society for Rheumatology. I note that the deadline for submissions is 10th May 2007. Please contact me if you require any additional information.

Drugs for the treatment of pulmonary arterial hypertension – contributing to the technology appraisal process

This submission has been prepared on behalf of the ***British Society for Rheumatology*** (BSR)

Yours faithfully

[redacted]

Email:

Department of Medicine (Hampstead Campus)
Royal Free & University College Medical School
Rowland Hill Street
London NW3 2PF, UK
Tel:
Fax:
Email:
Web: http://www.ucl.ac.uk/medicine/rheumatology-RF/

Drugs for the treatment of Pulmonary Arterial hypertension – contributing to the technology appraisal process

Prepared on behalf of the ***British Society for Rheumatology*** (BSR) 7th May 2007 by

[redacted]
Royal Free Hospital
London NW3 2QG

Email: [redacted]
Tel/Fax [redacted]

This submission focuses upon the technologies and applications related to pulmonary arterial hypertension (PAH) that are of particular relevance to the BSR and its members. Pulmonary arterial hypertension is recognised to occur in association with connective tissue disease. This comprises the largest single group of associated PAH as designated in the 2003 Venice Classification. Of the connective tissue diseases (CTD) systemic sclerosis (SSc) is the most frequently associated, with registry estimates derived from several studies suggesting that between 8 and 12% of cases of SSc may develop PAH. In addition other causes of elevated PAP occur in SSc, most notably left ventricular diastolic dysfunction and hypoxia induced PH secondary to severe interstitial lung fibrosis. In addition, it is frequent for some interstitial lung fibrosis to be present in cases with PAH. There are a number of studies suggesting that whilst the histological features and pathogenesis of PAH in SSc may be similar to idiopathic PAH, outcome is much worse in terms of survival. In addition cases of SSc with PAH may perform worse in assessment tests of exercise capacity for reasons other than PAH and this may confound assessment. Other CTDs are associated with PAH including SLE and overlap CTD – sometimes termed mixed connective tissue disease (MCTD). These groups appear to have a better outcome than SSc-PAH in published studies and also in recent analysis of pooled data from the UK PAH centres. The high frequency of PAH in SSc makes this an important complication. Review of the causes of death in SSc at our own centre confirms that PAH is the single largest cause of SSc-related mortality – contributing significantly to the 40% of SSc related death attributable to pulmonary complications. Screening is recommended in the management of all cases of SSc. For SSc algorithms have been developed that incorporate clinical and investigational features suggesting the possible presence of PAH. These lead to confirmation of the diagnosis by right heart catheterisation. At present this is essential. A vasodilator challenge is performed in other forms of CTD but not in SSc due to the negligible benefit observed for treatment with calcium channel blockers.

Overall, there has been a substantial improvement in outcome for PAH associated with SSc over the past 10 years. Thus published survival data from earlier studies are now much worse than current data. The availability of oral agents (initially endothelin receptor antagonists) has coincided with substantial improvement in survival. This has been demonstrated clearly in registry data published from our own centre [Williams et al 2006]. These improvements may reflect advances in pulmonary hypertension care including earlier supportive therapy and a

multidisciplinary team approach but the major treatment intervention that has been available is oral therapy. Nevertheless, outcome remains poor compared with iPAH. Survival data from our own SSc cohort confirm improvement in SSc. This includes better outcome in class II cases – probably due to early initiation of licensed treatment once they progress into class III. The natural history of PAH in SSc is very poor – but it appears that achieving or maintaining favourable haemodynamics has a big impact on survival. Although data are derived from a registry rather than form prospective trials they provide some of the best data in support of efficacay. Often oral agents are used in combination.

Pulmonary hypertension, defined as an elevation in the mean pulmonary artery pressure > 25 mmHg at rest, occurs in both limited and diffuse cutaneous forms of SSc, and is a leading cause of mortality. The outcome in SSc-associated pulmonary hypertension is considerably worse than that of idiopathic pulmonary hypertension [Denton CP et al 2006]. This may reflect co-morbidity or differences in underlying pathogenetic mechanisms. In SSc, PAH due to intrinsic fibroproliferative abnormalities in the pulmonary vasculature, pathologically indistinguishable from idiopathic PAH, is most common, with a prevalence of approximately 10-15%. The second pattern of pulmonary hypertension occurs in association with pulmonary interstitial fibrosis, and is driven by hypoxia as well as the destruction of the pulmonary vascular bed. In addition, PAH in SSc also occurs in the context of pulmonary fibrosis, and typical histological appearance of PAH can be found in lung biopsies from SSc patients with lung fibrosis. Indeed, it has been suggested that it is coexistent vasculopathy that determines outcome and survival in many cases of SSc-associated pulmonary fibrosis.

Pulmonary arterial hypertension may remain asymptomatic until quite advanced. The initial symptoms include exertional breathlessness, and less often chest pain or syncope. In patients with SSc, PAH is typically discovered during regular monitoring with PFT, Doppler-echocardiography and ECG examinations. An isolated reduction in DlCO with preservation of lung volumes is suggestive of PAH. Definitive diagnosis requires exclusion of thromboembolic disease by ventilation: perfusion lung scan, spiral CT scan or pulmonary angiography, and hemodynamic demonstration of a mean pulmonary artery pressure >25 mmHg at rest or >30 mm Hg upon exercise. There is a strong correlation between peak pulmonary artery pressure estimated by Doppler-echocardiography and direct measurements at right heart catheterization, except when pulmonary artery pressures are in the 30-50 mmHg range. Cardiac catheterization is essential for the workup, because it allows the recognition of pulmonary venous hypertension and the precise determination of pulmonary vascular resistance, cardiac output (cardiac index) and pulmonary artery pressures. Serum levels of the N-terminal pro-brain natriuretic peptide (BNP) may be helpful for screening and monitoring PAH. The levels of serum BNP correlate with survival in patients with SSc-associated PAH [Williams et al, 2006].

While historically PAH was associated with a grave prognosis, substantial progress in its management has been achieved recently. The current focus in the evaluation is on early identification and determination of severity. The WHO/NYHA functional classification is useful for assessing the severity of PAH, and for treatment decisions. Exercise capacity, typically assessed by the distance walked in 6 minutes under standard conditions, has prognostic implications and is used for risk stratification. .

Oral anticoagulation, spironolactone, and oxygen supplementation when appropriate, are generally used as supportive therapy. Specific treatments for PAH are initiated only for relatively advanced disease (functional Class III or IV); earlier intervention may be advantageous and is under investigation . Treatment options for Class III PAH include oral ET-1 receptor blockade [Barst RJ et al 2004] and 5'-phosphodiasterase inhibition [Galie N et al, 2005]. Alternative therapies include inhaled and subcutaneous prostacylin analogues. Intravenous agents are generally reserved for patients with severe or advancing PAH.

Interpretation of evidence for the technologies being evaluated will be considered with respect to connective tissue disease associated PAH.

Bosentan

ET-1 is an endogenous peptide produced by the endothelial cells. It is a potent vasoconstrictor with mitogenic, proinflammatory and profibrotic action. Its actions are mediated by two highly specific receptors - ETA and ETB. Both have been found on the surface of vascular smooth muscle cells where they mediate vasoconstriction. ETA-receptors are also found on cardiac myocytes while ETB are expressed on normal endothelial cells but are also upregulated on a wide variety of cell types in disease states. ET-1 levels have been shown to correlate strongly with PVR, mean PAP and 6MWD in patients with idiopathic pulmonary arterial hypertension (iPAH). Levels are also increased in patients with SSc, particularly associated with diffuse subset, pulmonary involvement with PAH and renal crisis. Bosentan is a dual ET-1 receptor antagonist licensed for use in patients with PAH. This is based on two pivotal trials – AC-052-351 (study 351) and AC-052-352 (Bosentan: Randomised Trial of Endothelin Receptor Antagonist Therapy for Pulmonary Arterial Hypertension (BREATHE-1)). Study 351 was a double-blind, randomized, placebo-controlled trial including patients with either iPAH or PAH-SSc. 32 subjects were randomized to receive 62.5mg bosentan twice daily for 4 weeks followed by 125mg bosentan twice daily or matching doses placebo. There was a statistically significant increase in the 6MWT compared to baseline among the bosentan treated patients and no change among the subjects who received placebo. At 12 weeks there was statistically significant difference between the mean 6MWD in the two groups with increase of 70m among the bosentan treated subjects and decrease of 6m among the patients on placebo ($p=0.021$) and this difference was maintained at week 20. Treatment with bosentan also significantly improved cardiac haemodynamics as assessed with cardiac catheterization, improved WHO functional class and increased time to clinical deterioration compared to placebo. Subsequently in a follow-up open-label study it was demonstrated that at 6 months the bosentan-treated patients maintained the improvement in 6MWD. In a bigger trial (BREATHE-1) Rubin et al. compared two doses of bosentan (125mg and 250mg twice a day) with placebo in 213 patients. At 16 weeks there was statistically significant difference in terms of 6MWT between the combined bosentan treated groups and the group receiving placebo ($p<0.001$), with improvement in the Borg dyspnea index, WHO functional class and time to clinical worsening of the disease among the bosentan treated patients. Both study 351 and the BREATHE-1 trial included patients with iPAH and PAH associated with connective tissue disease (PAH-CTD) with the majority of the patients having iPAH. To assess the role of bosentan in the treatment of PAH-CTD the subgroups of patients with CTD who participated in the two trials and their open-label extensions were pooled and analyzed. Overall 66 patients with PAH-CTD were randomized to participate in

the two major trials (44 were treated with bosentan and 22 received placebo). The actively treated patients showed stabilization in their exercise capacity while there was deterioration in the placebo group demonstrated by reduction in the 6MWD, although the difference between the two groups did not reach statistical significance. There was also a trend to delayed disease progression among the bosentan treated patients with increase of time to lung transplantation, hospitalisation for pulmonary hypertension, lack of clinical improvement or PAH worsening leading to discontinuation, need for epoprostenol treatment or atrial septostomy. These results are congruent with those obtained in a recent retrospective cohort study comparing survival and haemodynamic outcome of cases of PAH-SSc treated with first line bosentan and those treated previously. There was a significant advantage in the bosentan treatment era compared with this historical comparator group.

Sitaxentan

Antagonists that are selective for ETA have also been developed and evaluated as potential therapy for PAH. This is in part based upon the possibility that blocking ETA may have greater effect on the pulmonary vasculature than blocking both receptors. For example, ETB receptors were found to mediate vasodilatation through NO synthesis and were demonstrated to be essential for the pulmonary clearance of ET-1. The potential benefit from ETB receptor activation led to the development of selective ETA receptor blockers. Sitaxsentan To Relieve Impaired Exercise (STRIDE-1) was a double-blind, placebo-controlled trial of 178 patients randomized to receive placebo, sitaxentan 100mg or 300mg once a day for 12 weeks. The primary outcome was the change in percent of predicted peak O2 consumption during exercise with change in 6MWT and NYHA functional class being secondary outcomes. At 12 weeks there was statistically significant increase in the peak O2 consumption among the patients receiving 300mg of sitaxentan but no improvement among the patients receiving sitaxentan 100mg or placebo. Nevertheless there was significant improvement in the 6MWD in both sitaxentan-treated groups compared to placebo with no significant difference between the patients receiving 100mg and 300mg of the drug. The mean PAP improved after 12 weeks of treatment with the 300mg dose compared to placebo, but there was no significant improvement in the 100mg dose group. Pulmonary vascular resistance was significantly improved in both actively treated groups and both doses of sitaxentan improved the functional class of the patients compared to placebo. As STRIDE-1 trial included milder cases with PAH with no restriction for baseline 6MWD, patients with class II breathlessness and some patients with PAH due to congenital heart disease, the STRIDE-1 study group presented analysis of a subgroup of patients participating in the trial who met more rigorous inclusion criteria: those with iPAH or PAH-CTD, in WHO functional classes III and IV at baseline, with a baseline 6MWD< 450m. The analysis demonstrated even greater benefit from sitaxentan compared to placebo in terms of 6MWD, mean PAP, pulmonary vascular resistance and WHO functional class improvement. Analysis of the safety data from the STRIDE-1 trial showed that headache, peripheral edema, nausea, nasal congestion, and dizziness were the most frequent side effects. In addition increase in the aminotransferases values of >3 times the upper limit of normal was much higher for the 300mg dose compared to the 100mg dose. Analysis of the data from the extension trial which randomized patients to receive either 100mg or 300mg sitaxentan revealed that the cumulative risk of an aminotransferase value >3 times the upper limit of normal at 6 months was 8% for the 100-mg group and 26% for the 300-mg group and at 9 months it remained 8% for the 100-mg group but

increased to 32% for the 300-mg group. These results led to the conclusion that 100mg is the optimal dose for sitaxentan and in order to assess efficacy of this dose compared to placebo the STRIDE-2 trial was set. This was a randomized, double-blind, placebo-controlled trial that included 245 patients who were randomized to receive placebo, sitaxsentan 50 mg, or 100 mg once daily for 18 weeks. For observation only an open label bosentan arm was added. There was a statistically significant improvement in 6MWD among the patients receiving 100mg of sitaxentan and the open-label bosentan group with improvement which did not reach statistical significance in the group receiving 50mg sitaxentan. WHO functional class also improved significantly in the 100mg dose group with no significant change in the 50mg group and the bosentan group compared to placebo. Time to clinical deterioration showed a trend towards improvement in the group receiving sitaxentan 100mg and did not change compared to placebo in the 50mg sitaxentan group and the bosentan treated group. Liver transaminase >3 times the upper limit of normal were observed in 6% of the placebo group, 5% in the sitaxsentan 50 mg, 3% in the sitaxsentan 100-mg, and 11% for the bosentan receiving group. Sitaxentan appeared to be marginally better than bosentan in terms of improvement of 6MWT and time to disease worsening and is the second ET-1 receptor blocker licensed for treatment of PAH. Ambrisentan is another selective ETA antagonist currently being evaluated in two randomized, double-blind, placebo-controlled trials assessing safety and efficacy of three different doses of the drug against placebo. Although preliminary data is encouraging, the final results of the two trials have not been published yet.

Sildenafil

Cyclic guanosine monophosphate (cGMP) mediates the pulmonary vasodilating effect of nitric oxide and is degraded in the lung mostly by PDE5. Sildenafil selectively inhibits PDE5 and thus increases the levels of cGMP and enhances nitric oxide mediated vasodilatation. The efficacy of sildenafil for treatment of PAH was tested in a 12-week double-blind, placebo-controlled trial (Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study). 278 patients were randomized to receive placebo or sildenafil in dose of 20mg, 40mg or 80mg three times a day. There was statistically significant improvement in 6MWD, PAP, pulmonary vascular resistance and WHO functional class at 12 weeks in all sildenafil-treated groups compared to placebo, but no significant change in Borg dyspnea score and time to clinical worsening. Badesch et al. did a subgroup analysis of the 84 patients with CTD participating in the SUPER study. The results showed that sildenafil improves exercise capacity, WHO functional class and cardiac haemodynamics compared to placebo although clear benefit was observed only with the lowest dose of 20mg three times a day. The SUPER study showed that sildenafil is relatively safe and effective agent for treatment of PAH. In the Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) study 26 patients were randomized to receive either bosentan 62.5mg twice daily for 4 weeks followed by 125mg twice daily for 12 weeks or sildenafil 50mg twice daily for 4 weeks followed by sildenafil 50mg three times a day. There was no significant difference between the two groups in terms of right ventricular mass change, exercise capacity and change in N-terminal pro-brain natriuretic peptide levels. Sildenafil is now licensed for the treatment of PAH. Two other PDE5 inhibitors (Tadalafil and Verdenafil) have been candidates for treatment of PAH and the Tadalafil in the Treatment of Pulmonary Arterial Hypertension (PHIRST-1) trial is currently recruiting patients.

Iloprost

Currently the only inhaled drug which is licensed for the treatment of PAH is iloprost. Its use was ascertained in a large study of 203 patients who were randomized to receive either iloprost or placebo as an inhalation for 12 weeks. Iloprost significantly improved 6MWD, haemodynamic values and NYHA functional class. The placebo-treated patients were significantly more likely not to complete the study due to death or clinical deterioration. Beraprost, an oral prostacyclin analogue, was recently evaluated as a potential therapeutic option in PAH patients. Although the initial 12 week randomized, double-blind, placebo-controlled trial showed promising results, further evaluation in a longer 12 month study did not show any sustained benefit at 9 and 12 months. Currently the prostacyclin analogues licensed for use in PAH are iv epoprostenol and inhailed iloprost.

Treprostinil

In a series of trials iv treprostinil was compared initially to iv epoprostenol, then to sc treprostinil and finally sc treprostinil was compared to placebo in a double-blind fashion. The results revealed that treatment with iv epoprostenol, iv treprostinil and sc treprostinil produce similar improvement in pulmonary haemodynamics. Subcutaneous treprostinil showed a trend to improve exercise capacity and pulmonary haemodynamics although compared to placebo the changes were not statistically significant. In a much larger double-blind, placebo-controlled trial 470 patients were randomized to receive either continuous sc treprostinil or placebo on background of conventional therapy for 12 weeks. There was significant improvement in 6MWD and Borg dyspnea score among the actively treated patients compared to placebo with significant improvement in pulmonary haemodynamics (PAP, right atrial pressure (RAP) and PVR). Oudiz *et al.* analyzed the subgroup of patients participating in this study who had SSc demonstrating significant reduction in PVR in the actively treated group compared to placebo. There was also a trend in favor of treprostinil in terms of improvement in the other pulmonary haemodynamical parameters and 6MWD although they did not reach statistical significance. Most recently in a retrospective multi centre analysis Lang *et al.* demonstrated that the benefits from sc treprostinil treatment were maintained with significant improvement in 6MWD, Borg dyspnea score and functional class after a mean period of 26 months]. The longer half-life of treprostinil makes serious complications due to sudden interruption of treatment less likely. The possibility of giving inhaled treprostinil was examined in series of randomized, open-label single-blind studies comparing inhaled treprostinil to inhaled iloprost at comparable doses and exploring the highest possible inhalation dose and the shortest possible inhalation time. Both iloprost and treprostinil led to comparable level of reduction in PVR although treprostinil had significantly longer effect and fewer adverse reactions. The results suggest that inhaled treprostinil may be potentially useful for treatment of PAH.

Epoprostenol

Endogenous prostacyclin is a potent vasodilator and suppressor of platelet aggregation normally produced by the endothelial cells. Exogenous prostacyclin analogues emerged in the early 90s and currently there are three drugs licensed for treatment of PAH. Initially in a 12-week prospective, randomized, open-label trial of 81 patients addition of continuous iv epoprostenol to conventional therapy (anticoagulants, vasodilators etc.) was compared to conventional therapy alone [5]. There was significant improvement in exercise capacity and haemodynamics (pulmonary arterial

pressure (PAP) and pulmonary vascular resistance (PVR)) with significant reduction in mortality. Later Badesch et al. in a prospective, randomized, placebo-controlled trial of 111 patients showed similar findings in patients with scleroderma-associated PAH (PAH-SSc) with significant improvement in exercise capacity measured by 6-minutes walking distance (6MWD) and improvement in haemodynamics, functional class and Borg dyspnea score with a trend in favour of the iv epoprostenol-treated patients. Long term data presented by McLaughlin showed significantly improved survival in patients treated with epoprostenol (87.8%, 76.3%, and 62.8% at year 1, 2 and 3) compared to expected survival based on historical data (58.9%, 46.3%, and 35.4% respectively). Epoprostenol is delivered through a central vein as a continuous infusion necessitated by its short half-life and interruption may lead to a rapid symptomatic deterioration which can be life-threatening. This makes treatment with the drug complicated and it is recommended that patients requiring it should be referred to specialized centers.

Concluding remarks:

Clinical practice in the field of connective tissue diseases has been transformed by the availability of therapies for advanced pulmonary arterial hypertension. There have been substantial improvements in survival in association with the availability of the technologies under appraisal. Lives are transformed and patients have far better functional ability and reduced symptoms in most cases. This complication is not curable but in common with renal crisis in scleroderma can now be considered treatable. Although the absolute gain in survival is often below that seen in idiopathic PAH for patients with a chronic incurable and life-threatening disease the benefit of therapy for PAH in the context of connective tissue disease has been enormous.

Key supporting references:

- Wigley FM, Lima JA, Mayes M et al. The prevalence of undiagnosed pulmonary arterial hypertension in subjects with connective tissue disease at the secondary health care level of community-based rheumatologists (the UNCOVER study). Arthritis Rheum. 2005; 52(7):2125-32.
- Badesch DB, Tapson VF, McGoon MD et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. Ann Intern Med. 2000 Mar; 132(6):425-34.
- A seminal study that shows that scleroderma associated pulmonary hypertension benefits from epoprostenol. Survival benefit was not seen, unlike in the earlier primary pulmonary hypertension trial.
- Oudiz RJ, Schilz RJ, Barst RJ et al. Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. Chest. 2004; 126(2):420-7.
- Olschewski H, Simonneau G, Galie N et al. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med. 2002;347(5):322-9.
- Channick RN, Simonneau G, Sitbon O et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet. 2001; 358(9288):1119-23.
- Rubin LJ, Badesch DB, Barst RJ et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med. 2002; 346(12):896-903.
- Denton CP, Humbert M, Rubin L, Black CM. Bosentan treatment for pulmonary arterial hypertension related to connective tissue disease: a subgroup analysis of the pivotal clinical trials and their open-label extensions. Ann Rheum Dis. 2006; 65(10):1336-40.
- Williams MH, Das C, Handler CE, et al. Systemic sclerosis associated pulmonary hypertension: improved survival in the current era. Heart. 2006; 92(7):926-32.
- Barst RJ, Langleben D, Frost A et al. Sitaxsentan therapy for pulmonary arterial hypertension. Am J Respir Crit Care Med. 2004; 169(4):441-7.
- Galie N, Ghofrani HA, Torbicki A et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005; 353(20):2148-57.
- MacGregor AJ, Canavan R, Knight C et al. Pulmonary hypertension in systemic sclerosis: risk factors for progression and consequences for survival. Rheumatology (Oxford). 2001; 40(4):453-9.
- Williams MH, Handler CE, Akram R et al. Role of N-terminal brain natriuretic peptide (N-TproBNP) in scleroderma-associated pulmonary arterial hypertension. Eur Heart J. 2006; 27(12):1485-94.