



## **PHARMAC responds on treatments for pulmonary arterial hypertension**

Dr Ken Whyte recently wrote about the funding of medicines for rare life-threatening diseases (high-cost treatments for ‘orphan diseases’), using the example of bosentan for pulmonary arterial hypertension (PAH) (<http://www.nzma.org.nz/journal/118-1226/1759>).<sup>1</sup> He raises difficult issues that need discussion.

### **Treatments for PAH**

Subsidised access to high-cost treatments for PAH (such as iloprost, bosentan and high-dose sildenafil<sup>2</sup>) had since 2001 been initially provided under the Community Exceptional Circumstances (CEC) scheme ([http://www.pharmac.govt.nz/exceptional\\_circumstances.asp](http://www.pharmac.govt.nz/exceptional_circumstances.asp)). Over that time applications were relatively rare, no more than a few per year.

However, the CEC scheme requires rarity, i.e. that the prevalence of a condition is limited to no more than 10 cases nationally. During 2004 it became apparent that the rarity limit would be significantly exceeded (28 patients are now funded for high-cost PAH treatments, many on sildenafil<sup>2</sup>). Under the limits of the CEC scheme, PHARMAC was no longer able to approve applications for high-cost PAH treatments under CEC. PHARMAC therefore moved to find a permanent solution to the funding of PAH treatments.

The Pharmacology and Therapeutics Advisory Committee (PTAC) has noted a lack of information and a number of dilemmas with the management of PAH, and made a high priority recommendation that funding issues be resolved as soon as possible. PHARMAC is actively working on this. The relevant portions of the minutes of the two relevant PTAC meetings can be found in the Appendix to this letter.

Until a permanent solution is found, applications for new patients can still be made for subsidised treatment through the Hospital Exceptional Circumstances (HEC) scheme. Unlike CEC, HEC does not have a rarity criterion, but requires that treatment is cost-saving to the District Health Board (DHB). Since mid-2004, 19 patients have received approval for the use of high-cost PAH treatments under the HEC scheme, with more applications being received and approved every week.

Treatments for PAH are expensive, and annual treatment costs for each patient vary substantially between medications, with \$90-180,000 for iloprost, \$56,000 for bosentan and \$20-30,000 for sildenafil. Current DHB expenditure on high-cost PAH treatments is some \$600-700,000 per year, and the number of patients seeking treatment continues to grow.

The evidence for bosentan, iloprost and sildenafil also continues to grow. The recently published SUPER trial,<sup>3</sup> referred to by Dr Whyte, and the SERAPH study<sup>4</sup> indicate that sildenafil may be as effective as the more expensive bosentan.<sup>5</sup> Neither high-dose sildenafil nor nebulised iloprost is registered in New Zealand for use in PAH.

In response to Dr Whyte's comments about the cost-effectiveness of PAH treatments, we find it difficult to comment on the one published economic analysis on PAH (Highland et al 2003)<sup>6</sup> that we<sup>7</sup> and he can locate, which did have important limitations.<sup>8</sup> Economic analyses for individual PHARMAC CEC funding decisions have indicated that all three treatment options may be cost-effective as a bridge to transplantation, but perhaps the only cost-effective maintenance treatment for patients ineligible for transplant is sildenafil. Funding a medicine in Australia does not necessarily mean convincing cost-effectiveness—for instance, Australia continued to fund COX-2 inhibitors despite dubious cost-effectiveness.<sup>9</sup>

### **Prioritisation of very high cost medicines**

In general terms, PHARMAC's prioritisation process tries to allocate scarce resources in a fair way.<sup>10</sup> There are very expensive treatments that may offer significant benefits to a small number of people. Such very expensive treatments have to compete for limited funds with less expensive medicines that treat large numbers and achieve greater population health gains<sup>11</sup> for the same total costs. The growing number of costly new treatments makes such decisions both more common and more difficult.

PHARMAC is currently reviewing its decision-making process for high-cost medicines—driven in part by having to turn down treatments for small numbers of people who then miss out because there are no alternative treatments. This is where, even after assuming 100% effectiveness with large clinical benefits, the cost of these medicines is very high (at times \$250,000 per patient year or more). Funding them would deny treating too many people with other diseases.

PHARMAC's Board intends to consider the outcome of this review process next year; prior to that, any proposed changes to our decision-making processes would undergo public consultation.

That said, PHARMAC is actively working to permanently solve the funding of PAH treatments, independent of the high-cost review process.

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**Conflict of interest:** Scott Metcalfe is externally contracted to work with PHARMAC for public health advice. Dilky Rasiah and Sean Dougherty declare no conflicts.

## References and endnotes:

1. Whyte K. PHARMAC not funding some treatments for rare, life-threatening diseases: bosentan as an example. *N Z Med J*. 2005;118(1226). URL: <http://www.nzma.org.nz/journal/118-1226/1759>
2. As of 5 December 2005, 28 patients were funded for PAH treatment through Exceptional Circumstances—five were using iloprost, two bosentan, 20 sildenafil, and one vardenafil. Eleven of the patients had been approved sildenafil after being declined iloprost or bosentan. A further five patients had been declined any of the PAH treatments. In addition, many patients will receive iloprost for acute treatment as inpatients. Annual expenditure on high-cost PAH treatments is currently around \$600-700,000, with a roughly 20:80 split between community and hospitals. Most of the expenditure is on iloprost, either as acute in-hospital use or through EC (where the injection is nebulised).
3. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*. 2005;353:2148–57. <http://content.nejm.org/cgi/content/full/353/20/2148>
4. Wilkins MR, Paul GA, Strange JW, et al. Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) study. *Am J Respir Crit Care Med*. 2005;171:1292–7. Epub 2005 Mar 4. Abstract at <http://ajrccm.atsjournals.org/cgi/content/full/171/11/1292>
5. SERAPH is a head-to-head trial comparing sildenafil with bosentan that suggests that sildenafil is not demonstrably inferior to bosentan—although the primary measure was debateable and there was one death in the sildenafil group. High-dose sildenafil is not yet registered in New Zealand for PAH, but has recently been registered in the US for ‘the treatment of pulmonary arterial hypertension (WHO group 1) to improve exercise ability’.
6. Highland KB, Strange C, Mazur J, Simpson KN. Treatment of pulmonary arterial hypertension: a preliminary decision analysis. *Chest*. 2003;124:2087–92. <http://www.chestjournal.org/cgi/content/full/124/6/2087>
7. TRIP search <http://www.tripdatabase.com/> 9 December 2005 keywords pulmonary hypertension; PubMed searches 9 December 2005 keywords pulmonary hypertension AND (cost effectiveness OR quality adjusted life years OR cost utility or economic)
8. The Highland et al 2003 economic analysis compared bosentan with treprostinil and epoprostenol—neither used in New Zealand—in a South Carolina cost context. They did not examine sildenafil or nebulised iloprost, and relied on indirect comparisons; there were no head-to-head comparisons, and the trial data available were sparse, compounded by quite different eligibility criteria. Useful comment on this economic analysis can be found on the NHS CRD website at <http://nhscrd.york.ac.uk/online/nhseed/20040088.htm>
9. Grocott R, Metcalfe S. Going against the flow: the impact of PHARMAC not funding COX-2 inhibitors for chronic arthritis. *N Z Med J*. 2005;118(1223). URL: <http://www.nzma.org.nz/journal/118-1223/1690/>
10. Metcalfe S, Dougherty S, Brougham M, Moodie P. PHARMAC measures savings elsewhere to the health sector. *N Z Med J*. 2003;116(1170). URL: <http://www.nzma.org.nz/journal/116-1170/362/>
11. PHARMAC. A prescription for pharmacoeconomic analysis (version 1.1). September 2004. URL: <http://www.pharmac.govt.nz/pdf/pfpa.pdf>

## **Appendix: PTAC minutes relating to PAH**

### **Relevant record from the Pharmacology and Therapeutics Advisory Committee meeting 19 August 2004**

#### **“17 Management of Pulmonary Hypertension**

The Committee reviewed the literature presented by PHARMAC staff on pulmonary hypertension (PAH), which included a number of articles sourced by the discussion leader. Members agreed, in general terms, with the management course for pulmonary hypertension outlined in the PTAC paper submitted by PHARMAC staff.

The Committee discussed the strength and quality of the evidence presented for iloprost, bosentan and high-dose sildenafil for the treatment of PAH. The Committee noted that all the randomised controlled trials involving either iloprost, beraprost, bosentan or sildenafil for use in PAH were relatively small, of short duration and confined to adults. Members noted that the studies illustrated varying degrees of short-term (up to 6 month) improvements in six-minute walking test results or exercise times. Members were advised that there were two recent studies reporting long-term efficacy and survival rates with bosentan, but they did not have the chance to see the source publications to evaluate the robustness and relevance of the data. They noted that none of the medications iloprost, beraprost, sildenafil or bosentan were without adverse effects.

The Committee noted that only iloprost has a registered indication for PAH in New Zealand. Members also noted that there are other therapies being trialled overseas for PAH which include sitaxsentan and ambrisentan (selective endothelin A antagonists) and combination therapy. Members also noted the use of inhaled nitric oxide and arginine, but there have been no RCTs of their use in PAH.

The Committee considered that the patients who benefit the most from iloprost, sildenafil or bosentan are those with primary pulmonary hypertension, and considered that the evidence for secondary PAH was not as clear. Members noted that there were no documented differences in incidence and prevalence rates of PAH between Maori and Pacific people and others, and considered that overall numbers of patients were too low to detect statistically meaningful differences.

The Committee noted that Australia's Pharmaceutical Benefits Scheme funds bosentan with restrictions, and that, if bosentan were funded on the Pharmaceutical Schedule, then similar or even stricter criteria (for instance only for primary PAH or only as a bridge to transplantation) could be used for any or all of the newer PAH treatments.

Members noted that the use of these treatments would result in additional non-medication expenditure to the health sector, as frequent investigations would need to be undertaken to monitor effects of treatment.

They also noted that the economic analyses, and the rapid cost-utility analyses (CUAs) and board papers that have been completed to assess individual patients for Community Exceptional Circumstances (CEC) funding, highlight the difficulties inherent in making decisions regarding PAH funding. These include:

- The treatments are very expensive:

- A number of patients are already funded via CEC;
- Patient numbers now exceed the CEC rarity criterion;
- Given the cost, cost-effectiveness is likely to be very poor;
- Current treatment options suggest improvement in exercise tolerance and haemodynamics, but there is no evidence to date for any improvement in survival;
- Given the lack of systematic survival data, significant assumptions and extrapolations are required in any CUA analyses.

The Committee noted that, often when there is very little long-term or endpoint data, members would not consider the funding issue further until such data had been provided. However, for the following reasons, they considered that this situation needed further consideration at this time:

- Difficulty in separating the pharmaceutical treatments for PAH from heart/lung transplantation aspects of therapy that are already happening;
- CEC being asked to fund patients already started on treatment, and the ethical issues faced in withdrawing government funding in this situation;
- CEC already funding a number of patients but rarity criterion having now been exceeded;
- The significant number of case studies indicating increased survival.

The Committee considered that, as new patients no longer meet the CEC criteria, it would be unacceptable to recommend an option that did not consider applications for new patients. Similarly it would not be acceptable to defer a decision until endpoint data and registration were available.

PHARMAC staff presented various funding options to the Committee:

- the status quo;
- disease state management panel funding; and
- HEC funding.

With potentially 120-200 patients with severe PAH in New Zealand, members did not consider it was an option to have future funding via CEC from a budgetary perspective, because of delays (turnaround time) and breaching of the CEC rarity criterion. They considered that the EC panel, with the number of applications it had now considered, did have the required expertise (with expert opinion sought if required) to consider PAH treatment applications.

The Committee noted that HEC management was consistent with an approach that PAH treatment is part of an overall treatment package that may or may not include transplantation. However, given the small size of some DHB budgets (from where HEC funding would come)—and hence the risk that patients domiciled in smaller DHBs may not even be referred to HEC for consideration of funding—HEC management may not be a long-term option. However, the Committee also discussed the possibility of the lead DHB, i.e. the transplant assessment units, funding the treatment, such that HEC could be a longer-term option. There was also some discussion about the possibility of a national protocol (or similar) for these products,

formulated by experts in the field, which HEC could administer in collaboration with DHBs.

The Committee considered that the disease state management panel option might be the best option long-term. Members envisaged that such a panel would manage the patient throughout the whole process, from consideration of conventional treatments and suitability for transplantation through to use of newer treatments. The Committee had concerns about budget overruns, and that a panel consisting solely of experts in the area would cause potential conflicts of interest as they would most likely also be the clinicians managing the patients. They recommended that any such panel would need to operate within a set budget and would consist of experts in the area together with PTAC and/or EC panel members. The Committee recommended that such a panel should act within strict protocols outlining how long treatments would be tried before being abandoned. Members noted that such an overview approach is not possible currently under CEC for the reasons outlined above. They noted that, within the protocols, the PAH panel would have the flexibility to manage the patients, so that any required trade-offs could and would need to be made in order for the panel to stay within budget.

The Committee **recommended** that applications for PAH treatment be considered via HEC in the interim, while PHARMAC staff explore the possibility of other options, including funding treatments via a disease state management panel. PTAC gave this recommendation a high priority, and asked that the funding issue be resolved as soon as practicable.”

#### **Relevant record from the Pharmacology and Therapeutics Advisory Committee meeting 17 February 2005**

“Two applications have been received for consideration:

- 1) Bosentan (Tracleer), submitted by Actelion Pharmaceuticals Australia and Asia Pacific (January 2005)
- 2) Iloprost (Ilomedin), submitted by Schering NZ Limited (October 2004)

#### **14. Bosentan (Tracleer)**

The Committee noted that the PHARMAC Board had considered a paper on the management of PAH at its 15 December 2004 meeting and had directed PHARMAC staff to seek Pharmaceutical Schedule applications.

The Committee noted that bosentan and iloprost are currently funded via the Hospital Exceptional Circumstances (HEC) scheme, as the rarity threshold for Community Exceptional Circumstances (CEC) has been exceeded.

The Committee noted that there is an estimated prevalence of 120-200 patients with PAH in NZ (using UK prevalence data), of whom only 10-25% would be likely to respond to calcium channel blockers.

The Committee noted that bosentan has received provisional registration with Medsafe in December 2004, pending further information from the company.

The Committee noted that apart from the Channick et al (2001) and Rubin et al (2002) randomised controlled trials, the only other evidence of note were open-label

extension studies by Sitbon et al (2003) and Roux et al (2001), which looked at the long term safety and efficacy of bosentan, and an open-label longitudinal study by Barst et al (2003) which looked at the safety and efficacy of the drug in paediatric patients with PAH.

The Committee considered that bosentan demonstrated subjective and objective improvements, especially in terms of exercise tolerance, haemodynamic parameters and New York Heart Association (NYHA) functional class. It also considered that outcomes were likely to be better in patients with primary PAH than in those with PAH secondary to connective tissue/collagen vascular disease, although this had not been shown statistically. Members considered that bosentan did not demonstrate clear end point advantages over other unlisted treatments such as nebulised iloprost, sildenafil, or sitaxsentan, although they noted that comparative data was limited. The Committee considered that bosentan represented an advance on currently funded treatments on the Pharmaceutical Schedule such as warfarin, diuretics, and calcium channel blockers. The drug also has an advantage in being orally administered.

The Committee considered that there were significant safety concerns regarding bosentan since the drug is associated with such risks as hepatotoxicity, (effects on CYP450), and potential teratogenicity.

The Committee noted that Actelion's cost projections may be underestimated because the company used US prevalence figures of 12.5 cases per million, whereas UK data suggests a prevalence of 30 to 50 cases per million.

The Committee considered that, in the absence of long-term observational studies, head-to-head studies, and studies using treatments in combination (eg. nebulised iloprost and sildenafil) that address efficacy, survival, safety, quality of life and costs, the approach to managing PAH would largely depend on regional experience, funding constraints, administrative regulations, clinical context and patient preference. The Committee noted that limited randomised controlled trial (RCT) data suggest that bosentan, nebulised iloprost and sildenafil have similar effects.

The Committee **recommended** that the option of a PAH treatment panel be pursued by PHARMAC. Based on the evidence so far supplied on bosentan, the Committee considered that the treatment could be funded through such a mechanism. Additionally, iloprost, sildenafil and other developing treatments for PAH could also be considered via this mechanism. It noted that the panel would need to operate under strict entry and exit criteria and a budgetary cap. The Committee noted that access to funding for PAH treatments, for those in whom it is appropriate, may currently be sought via Hospital Exceptional Circumstances.

On the basis of clinical evidence, the Committee **recommended** the listing of this treatment on the Pharmaceutical Schedule with a low priority, as the Committee was of the opinion that additional evidence on the use of this treatment in PAH, as outlined above, was required.

However, the Committee noted that there is a significant unmet need in these patients due to the severe nature of this disease, and that only a small proportion of patients can be successfully treated using standard treatments. Therefore, the Committee considered a high priority should be given to finding a method of funding treatments for PAH.

The relevant decision criteria are: (i) *the health needs of all eligible people within New Zealand;* (iii) *the availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* (v) *the cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services;* and (vi) *the budgetary impact (in terms of the Pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

### **15. Iloprost (Ilomedin)**

The Committee noted that the PHARMAC Board had considered a paper on the management of PAH at its 15 December 2004 meeting and had directed PHARMAC staff to seek Pharmaceutical Schedule applications.

The Committee noted that bosentan and iloprost are currently funded via the Hospital Exceptional Circumstances (HEC) scheme, as the rarity threshold for Community Exceptional Circumstances (CEC) has been exceeded.

The Committee noted that there is an estimated prevalence of 120-200 patients with PAH in NZ (using UK prevalence data), of whom only 10-25% would be likely to respond to calcium channel blockers.

The Committee noted that only iloprost IV is registered in New Zealand. This means that the use of the IV solution in a nebuliser to deliver iloprost in an inhaled form is an unregistered use.

The Committee considered that the evidence for nebulised iloprost was weak, and was no better or worse than for other treatment options in PAH. However, members considered that seriously ill patients (NYHA class 4) should probably be treated first with IV prostacyclin or nebulised iloprost or maybe sildenafil, as bosentan, beraprost and subcutaneous prostacyclins may not provide a significant clinical response for several weeks.

The Committee noted the Ghofrani et al (2002) study, looking at acute haemodynamic response, showed the combination of nebulised iloprost and sildenafil 50 mg could have synergistic effects.

The Committee considered that iloprost demonstrated subjective and objective improvements, especially in terms of exercise tolerance, haemodynamic parameters, and NYHA functional class. Members considered that nebulised iloprost did not demonstrate clear end point advantages over other unlisted treatments like bosentan, sildenafil, or sitaxsentan, although they noted that comparative data was limited. The Committee considered that iloprost represented an advance on currently funded treatments on the Pharmaceutical Schedule but noted that the frequency of nebulisations (6-9 times a day) may be inconvenient and may affect patient preference for treatment. The Committee also considered that iloprost has a few minor adverse effects but is generally well tolerated.

The Committee noted that Schering has suggested establishing a fund of \$500,000/year for the treatment of PAH, to be managed by a panel of 2-3 experts in the field instead of a listing under Special Authority.

The Committee considered that, in the absence of long-term observational studies, head-to-head studies, and studies using treatments in combination (e.g. nebulised

iloprost and sildenafil) that address efficacy, survival, safety, quality of life and costs, the approach to managing PAH would largely depend on regional experience, funding constraints, administrative regulations, clinical context and patient preference. The Committee noted that limited randomised controlled trial (RCT) data suggest that bosentan, nebulised iloprost and sildenafil have similar effects.

The Committee **recommended** that the option of a PAH treatment panel be pursued by PHARMAC. Based on the evidence so far supplied on iloprost, the Committee considered that the treatment could be funded through such a mechanism. Additionally, bosentan, sildenafil and other developing treatments for PAH could also be considered via this mechanism. It noted that the panel would need to operate under strict entry and exit criteria and a budgetary cap. The Committee noted that access to funding for PAH treatments, for those in whom it is appropriate, may currently be sought via Hospital Exceptional Circumstances.

On the basis of clinical evidence, the Committee **recommended** the listing of this treatment on the Pharmaceutical Schedule with a low priority, as the Committee was of the opinion that additional evidence on the use of this treatment in PAH, as outlined above, was required.

However, the Committee noted that there is a significant unmet need in these patients due to the severe nature of this disease, and that only a small proportion of patients can be successfully treated using standard treatments. Therefore, the Committee considered a high priority should be given to finding a method of funding treatments for PAH.

The relevant decision criteria are: *(i) the health needs of all eligible people within New Zealand; (iii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (v) the cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and (vi) the budgetary impact (in terms of the Pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*"