Submission to PBS Review of PH medicines

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Issues:

1) As with an increasing number of diseases, Pulmonary Hypertension fits into the category of an orphan disease. The fact that the commonest cause of pulmonary hypertension as opposed to pulmonary arterial hypertension is left heart disease (WHO group II) further confuses this field. Especially if one considers that in a proportion of patients with "passive" elevation of pulmonary pressures by left heart disease the elevated pressures appear to trigger the remodelling of small muscular pulmonary arteries (SMPA) and the development of pulmonary arterial hypertension.
2) In regards to pulmonary arterial hypertension then the heterogenous group of patients who develop this disease (WHO group 1) also clearly demonstrate further widespread heterogeneity in terms of their prognosis and response to pulmonary vasodilator medication. This appears to reflect a wide variability in the aggressiveness of the disease and consequent rate of obliteration of SMPA as well as quite dramatic variability in the human population of the ability of the right ventricle to cope with the excessive resistive and impedance loads placed on it by these diseases.
3) The result of this striking heterogeneity is that predicting prognosis and assessing the degree of response to therapy is difficult. I would contend as a result meaningful cost benefit analysis in this orphan disease has been to date impossible to determine in any of these groups of patients with any reliability or credibility.
4) It is thought that at the time of presentation with PAH considerably more than 50% of these crucial vessels, the small muscular pulmonary arteries have been damaged or obliterated. We have no convincing evidence that any of the currently available therapies can reverse that damage.
5) In some of these patient groups associated comorbidity, eg the scleroderma related PAH group, then the other impacts of their disease on functional capacity will limit the maximum achievable functional level despite a haemodynamic response to therapy. The haemodynamic response to therapy will off-load the RV and improve their prognosis despite the apparent lack of clear benefit in terms of function as measured by the six minute walk distance (6 MWD) for example.
6) Current management algorithms reflect a one size fits all approach as we do not have data sets to allow the development of a series of parallel treatment algorithms for individual patient groups. Such more specific algorithms may, for example mandate achieving WHO functional class II as the aim or therapy in a middle aged adult with idiopathic PAH and that initial (up front) or early escalation to combination therapy if not in WHO II should be standard of care. Whereas a 75 yr old with scleroderma and other comorbidities aiming for WHO II is unrealistic as issues other than

PAH are functionally limiting. In such a patient an algorithm could mandate to treat with monotherapy with the aim of achieving a limited improvement in functional class and stabilising their disease. Escalation to combination therapy would be indicated if and when there was any fall in functional ability or evidence of increasing RV dysfunction. The aim of combination therapy at this stage is preventing progressive RV impairment, increasing functional limitation and potentially prolonging life. Though we have to accept we have limited evidence of a mortality benefit with any therapy in PAH.

As PAH is an incurable disease, similar to many cancers and untreated with a prognosis worse than some cancers the approach in PAH treatment should be one of "disease control" so that patients can live with this disease and achieve a reasonable quality of life for a period before disease progression. This approach is now standard of care in the treatment of incurable cancers and the treatments to achieve such a goal are mostly funded despite their costs and limited cost effectiveness data.

In regard to trying to determine cost effectiveness for these medications in PAH I would like to illustrate the heterogeneity of both this disease and the response to therapy in this patient group with two illustrative case histories:

These are two young women who presented with life threatening idiopathic PAH in relation to pregnancy:

The first presented in extremis following delivery of her [redacted] child and the child had features of [redacted]. The mother had no clinical features or history to suggest [redacted] though had positive serology. She was treated initially with IV prostanoid in ICU and stabilised. As there was no funding for long term IV prostanoid therapy she was transitioned to inhaled iloprost for 6 months with clear improvement in pulmonary artery pressures. Again because of funding issues she was then given a trial of high dose calcium antagonist therapy but her pulmonary artery pressures increased again and she was restarted on inhaled iloprost. When bosentan became available she was then transitioned to monotherapy with this agent which successfully controlled her PAH for the next 12 years though she continued to have high pulmonary artery pressures on ® hearth catheter throughout her RV function improved very significantly as shown by her cardiac index. Late last year, over 18 yrs after first presentation we noted evidence of increasing RV dysfunction & falling 6 MWD and she has recently commenced combination therapy 18 yrs after her first presentation. She has never manifested any clinical features of SLE over those 19 yrs.

The second young woman was diagnosed early in pregnancy and elected not to have [redacted]. She had relatively mild PAH and was started on monotherapy at the end of the first trimester. As access to combination therapy was not guaranteed in New Zealand at that time [redacted] she was referred to the PH unit [redacted]. Her pregnancy progressed straightforwardly and her PH appeared

stable. Following delivery she deteriorated abruptly with RV decompensation. She was commenced on triple therapy with no improvement in her RV function and was transferred to a transplant unit for emergency listing but deteriorated and died before suitable lung grafts became available.

In connective tissue disease related (CTD) PAH the variability in response and duration of response is even more unpredictable. Rather than give a long list of patient summaries to prove this point I would point out some of the variability group by group:

- There are a group of patients with CTD related PAH within the larger group who see little objective response to therapy in terms of function and at most only marginal subjective benefit. However they are stable for a variable period on mono-therapy and then the disease progresses.

- When such progression occurs soon after starting mono-therapy one would expect both a limited functional response to combination therapy and only a limited period of stabilisation on combination therapy before further disease progression.

- Our experience of patients in this group over the last 20 yrs has been a wide variation both in response and duration of response. We have had several CTD related PAH patients who have had disease progression within a year of starting mono-therapy who have then stabilised for 3+ years and in some cases for more than 6 years.

- We have failed to identify any factor that reliably predicts this favourable therapeutic response to combination therapy.

- We have identified patients who have progressed to the point of developing advanced right heart failure due to RV decompensation as likely to have a poorer prognosis though even in that scenario some patients have such a sustained response to therapy that the RV manages to "re-group" and recover function (as occurred in the first woman above who presented post partum with advanced PAH).

- In many of these scenarios despite the heterogeneity of response patients have improved quality of life, accepting it is not returned to normal, and a significant period of disease "control".

- We have registry data from a number of countries that PAH populations treated with these agents have better outcomes compared to patients from previous era when there were either no therapies or very limited therapeutic options. However we lack placebo controlled RCT evidence of a mortality benefit as most physicians and ethics committees would see such a study as unethical in view of proven ability to improve quality of life, prolonging time to

clinical worsening, the recommendations of current international guidelines as regards standards of care and indirect evidence of significant survival benefit.

In summary we do have very strong reason to believe these drugs are effective but the heterogeneity of the patient groups, the variable response of patients within groups of what is a relatively rare set of diseases have made it impossible to produce robust cost effectiveness data to guide funders in developing clearly proven acceptable funding strategies.

Challenges in funding therapy for Pulmonary Arterial Hypertension:

1) Ensuring that these medications are only used in appropriate patients i.e. those in WHO group I and IV (chronic thromboembolic pulmonary hypertension). These are relatively small groups of patients whereas if there is "creep" of use into WHO group II and III (those with advanced respiratory disease) then the potential number of patients on therapy will increase dramatically.
2) Ensuring all appropriate patients have access to combination therapy at an appropriate stage of their illness with the aim to stabilise their condition first and foremost but also to prevent increasing RV dysfunction and avoid the risk of irreversible RV decompensation.
3) We have a range of proven therapies but no "head to head" studies comparing different therapeutic agents with each other either within sub-groups of agents e.g. ERA or between different sub-groups eg PDE-5 compared to ERA. We have increasing evidence of the benefits of combination therapy but very limited evidence regarding the most appropriate combination therapy or the most appropriate algorithm to achieve the maximum benefit for our heterogenous groups of patients.

Possible Models to ensure adequate access and appropriate use of these agents:

In different countries a variety of approaches have been used in an attempt to ensure appropriate use of these medicines. The UK has restricted their use to patients under the care of a group of specialised pulmonary hypertension units who have to follow agreed criteria around prescribing these medications. There is close auditing of the use of medications and outcomes.

As the number of patients being diagnosed in the UK has risen progressively with increasing detection of these diseases this approach gives the funders significant confidence that this increase is reflecting increasing diagnosis of PAH rather than "creep" of use of these drugs into other patient groups. Their data is available in annual reports going back over 10 yrs. This data demonstrates the relative consistency of number of patients requiring more complex therapies such as intravenous prostanoids with only a relatively small proportion of patients been deemed appropriate for these therapies.

In Belgium, Poland and New Zealand there are panels that review applications for access to these medications to ensure accurate diagnosis and appropriate use of medications including appropriate escalation of therapy to combination therapies. Similar to the UK these countries have seen a steady increase in numbers of appropriate applications over time. Whether such a system of "peer" review has limited inappropriate applications and thus "creep" is impossible to prove but has given funders some confidence that the medications are being used wisely.

The majority of European countries have listed funding criteria but do not actively review the appropriateness of usage in their countries.

Both the UK and NZ have outlined specified therapeutic pathways, eg in both countries a PDE-5 inhibitor is mandated as first line mono-therapy unless there is a clear contraindication. In UK sildenafil has been the recommended first line agent.

With some of these medications now coming off patent, eg sildenafil and bosentan, and in the absence of clear evidence that within each group of agents (PDE-5, ERA, nitric oxide pathway) no one compound is clearly better than another agent then mandating by funders of which agent in each category of pulmonary vasodilators should be first line could reduce the overall cost of treating each PAH patient significantly.

If this approach then allows earlier and wider access to combination therapy due to improved cost-effectiveness with cheaper agents then this approach would be totally defensible. There would have to be provision for access to other agents in each class of medications for patients who are intolerant of the "mandated" agents.

On the basis of current evidence this is a reasonable and defensible strategy to manage the financial "risk" and achieve the best possible outcome with available funding resources.

Another possible approach is "packages" of care for the treatment of PAH negotiated with a preferred provider, a pharmaceutical company with a range of PAH medications in its portfolio, that ensures that there is a ceiling of cost of therapy in a year for treating any PAH patient. Such a system would need reasonably accurate modelling of patient numbers and what proportion of patients would escalate and at what stage in their illness. For the pharmaceutical company it would involve them in risk sharing with the funder of "unexpected" numbers of patients presenting or of patients needing treatment escalation.

I would be happy to discuss this submission directly or any other issues the review panel wished to raise either as an individual practitioner with an interest and experience in treating these challenging diseases or in my role as President of the PHSANZ.

I have also listed below the specific issues that PHSANZ identified as central issues for the PBS Review and to be covered by the panel's terms of reference:

We would suggest the Terms of Reference are aligned and focused on specific areas to both allow equitable access to therapy across the country and to ensure appropriate use of these medicines to achieve the best outcomes for patients and effective use of resources.

1) the TOR should aim to align with current international guidelines with the recent ESC/ERS guidelines being an appropriate initial document to appropriately modify for the Australian funding environment. Specific issues that should be clearly included in the TOR are:
2) Access to medication for all patients in WHO group 1 PAH – this is based on the clear evidence that whilst the triggering event for the development of PAH may vary eg HIV or anorexant drugs, the pathobiology is identical within Group 1 and response to therapy is similar whatever the initiating event.
3) FC II patients have been included in many of the recent major trials of therapy and this group of patients have a similar response to therapy as FC III patients. Haemodynamic data in FC II patients has demonstrated very similar haemodynamics to FC III with the only distinguishing feature being better RV function ie the RV is still coping with the excessive load but a variety of sources have confirmed that FC II patients are at significant risk of early deterioration and progression to FC III. We also have evidence on the PAH registry that the number of FC II patients is relatively small (approximately 15%) and that "relaxing" access criteria will have limited impact on the number of patients on therapy. We would emphasise that the major issue remains late presentation of the majority of patients with this disease, the majority being in FC III and not infrequently in FC IV.
4) A number of recent large studies have demonstrated the benefits of combination therapy and we would propose that the TOR include access to funded combination therapy. Early sequential therapy for patients that fail to achieve an adequate improvement in symptoms and physiological markers of severity would be the approach that should be reviewed as part of the TOR. Again recent guidelines have provided guidance on outcome markers that can be used to both guide treatment decisions and avoid inappropriate use of the rapy. These studies have used TTCW/TTCF as endpoints and these are relevant endpoints for patients (avoiding events that lead to decreases in QOL) and relevant to the health system as these events lead to increased costs eg hospital admission.
5) Treatment by experienced clinicians with a specialist interest in pulmonary vascular disease has been shown to improve outcomes and ensure appropriate use of therapies as demonstrated in UK data stretching over 10 yrs. TOR should include review of the current practice which has led to 58 centres in Australia (UK has 7 and France 26 for much larger populations). which even allowing for the geographical challenges are difficult to defend. Despite our current system registry data does not suggest that there is excessive use of medication in comparison with UK and European registry data. However decisions on escalation of therapy require significant expertise and we would strongly support the TOR including a review of the

most effective method of ensuring prescribing is in the hands of experience clinicians. The overseas data also demonstrate that use of specialised centres has avoided overuse of medication by adherence to guidelines.

Finally we would encourage PBS to consider utilisation of the data in the PHSANZ registry in guiding their discussions and decisions. This data is collected with the purpose of improving patient care and is open to requests for specific analyses by a wide range of stakeholders in this area.

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