Pulmonary Arterial Hypertension Subcommittee of PTAC meeting

held 13 May 2010

(minutes for web publishing)

Pulmonary Arterial Hypertension Subcommittee minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*.

Note that this document is not necessarily a complete record of the Pulmonary Arterial Hypertension Subcommittee meeting; only the relevant portions of the minutes relating to Pulmonary Arterial Hypertension Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are published.

The Pulmonary Arterial Hypertension Subcommittee may:

(a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes were reviewed by PTAC at its meeting on 5 & 6 August 2010, the record of which is available on the PHARMAC website.

Contents

1 PAH of the newborn, including PAH secondary to chronic diaphragmatic hernia, chronic lung disease and other lung disease

1.1 The Subcommittee noted that the Pharmacology and Therapeutics Advisory Committee (PTAC) had considered a proposal regarding access to sildenafil for infants with PAH at its meeting on 7 May 2010. Although the minutes from that meeting were not available, the Subcommittee noted that PTAC had given sildenafil a high priority for funding and had deferred the application to the PAH Panel for further consideration.

Persistent pulmonary hypertension of the newborn (PPHN)

1.2 The Subcommittee noted that infants with PPHN essentially had a persistent foetal circulation post partum for a variety of aetiologies. The Subcommittee considered that these patients are often very sick and have a high mortality rate. Some patients also have a pronounced shunt.

1.3 The Subcommittee considered that the predominant cause of PPHN is meconium aspiration syndrome (MAS) which occurs in 20% of preterm newborns. Members considered that in infants with MAS, PPHN results from hypoxic vasoconstriction in the pulmonary vasculature, which is an acute, reversible lung insult. Members considered that infants with PPHN secondary to MAS or other acute lung injury could be differentiated from infants with PAH secondary to other chronic lung disease due to the reversible nature of the condition.

1.4 The Subcommittee noted that previously treatment of these infants had utilised extracorporeal membrane oxygenation (ECMO) and inhaled nitric oxide (iNO). Members noted that three to four years ago treatment with sildenafil became more common in these patients.

1.5 The Subcommittee noted that the Baquero study showed a treatment benefit with sildenafil in patients with a variety of aetiologies of PPHN, but that the trial was stopped early (Baquero et al, *Pediatrics*, 2006; 117:1077-83) as strongly positive.

1.6 The Subcommittee noted that in this patient group sildenafil would usually be given in hospital and that its use was becoming common in intensive care units where it is used at the upper dose range. Members considered that treatment would generally be required for less than three months in these patients and treatment would likely be stopped prior discharge. Members noted the PAH Panel is not seeing many applications for this indication because the majority of usage for this indication is in inpatients.

1.7 The Subcommittee considered that, should treatment as an outpatient be required, this patient group would meet the current funding criteria under the PPHN category, although, a recent echocardiogram showing evidence of PAH would be required for treatment to be approved.

1.8 The Subcommittee considered that sildenafil treatment in these patients may be cost effective as it may offset the cost of transporting infants between neonatal units.

Chronic diaphragmatic hernia (CDH)

1.9 The Subcommittee considered that infants born with CDH presented with a complicated clinical picture, including diaphragmatic and chest wall abnormalities, lung hypoplasia, and were difficult to intubate, sometimes also leading to tracheomalacia. Members noted that in some patients the liver plugs the hernia, resulting in milder disease in these patients, whereas in other patients the gut may enter the thorax leading to more severe disease. Members noted that surgery is now performed after birth to seal the herniation, but that some time may be taken to stabilise patients prior to surgery. The Subcommittee considered that a subset of patients with more severe disease are likely to require vasodilator treatment and are the patients that the PAH Panel is likely to receive applications for.

1.10 The Subcommittee considered that these infants are difficult to investigate for PAH. Echocardiograms may be technically difficult due to poor echo windows and it may not always be possible to obtain a tricuspid regurgitation (TR) jet. Members noted that sometimes septal flattening may be seen on echocardiogram.

1.11 The Subcommittee considered that due to the difficulties in investigating PAH in these infants, if there was any suggestion of PAH, patients were likely to be commenced on vasodilator therapy whilst still in hospital after birth.

1.12 The Subcommittee considered that performing a right heart catheter in these sick infants would not be without significant risk and therefore it would be difficult for the Subcommittee to mandate a cardiac catheter to be provided with initial applications.

1.13 The Subcommittee noted that there are now studies which include cardiac catheter data showing elevated pulmonary pressures in these patients, with pulmonary vascular and parenchymal anomalies. Members considered that there is a strong argument to provide vasodilator therapy to these patients.

1.14 The Subcommittee considered that measures of benefit could include six-monthly echocardiograms, oxygenation status and growth. Members considered that although it may be difficult to mandate a cardiac catheter with initial applications, it may be appropriate to recommend that a cardiac catheter be performed at 12 to 18 months for diagnostic and prognostic measures to develop a clear treatment strategy.

1.15 Members considered that given CDH has an incidence of one in 3,000 to 4,000 live births, and that 10 to 15 patients would be a reasonable estimate of patient numbers. Members noted that at present the PAH Panel is seeing less applications than this estimate.

1.16 The Subcommittee considered that the dose of sildenafil required for patients in this group would be 3 to 8 mg/kg/day, and that the average weight of patients would be 3 to 8 kilograms.

1.17 Members considered that treatment would likely be required for up to twelve months post-discharge in the majority of patients, but noted that some patients may require

1.18 Members considered that there was no alternative treatment for these patients and that sildenafil would reduce the time patients spend in hospital and would also result in a mortality and morbidity gain, but that these gains were difficult to quantify.

1.19 Members **recommended** that sildenafil be funded for PAH secondary to CDH with a high priority.

Chronic lung disease (CLD)

1.20 The Subcommittee considered that chronic lung disease is the leading cause of respiratory mortality in infants and affects most premature babies. Members noted that due to their respiratory compromise, these infants are fragile and require a high level of care. Members considered that these infants may be in hospital for three to four months, including several weeks in neonatal intensive care units.

1.21 The Subcommittee considered that infants born with chronic lung disease are usually oxygen dependant and often require respiratory support for at least the first month post-natally. Members considered that often clinicians find it difficult to wean these patients from ventilators so add sildenafil to aid in the weaning process. The Subcommittee considered that it is difficult to determine which of these patients may actually have documented PAH as opposed to simply being quite unwell.

1.22 The Subcommittee considered that it may be difficult to obtain a diagnosis of PAH in these infants. An echocardiogram is sometimes obtained to determine whether PAH is present, although a TR jet measurement may be variable and there may be difficulties in gaining a diagnosis. Members noted that access to echocardiography services differ throughout the country.

1.23 Members considered that cardiac catheterisation would not be appropriate in these patients, noting that patients may be too fragile to undergo anaesthetic. Members also considered that if cardiac catheters were required in these patients this may place an unnecessary strain on cardiac catheter resources.

1.24 The Subcommittee considered that once a patient has been commenced on treatment, patients would likely to be receiving both sildenafil and oxygen in the community and it becomes difficult for the clinician to determine when either treatment should be weaned.

1.25 The Subcommittee considered that measures of benefit could be similar to patients with PAH secondary to CDH, and could include six-monthly echocardiograms, oxygenation status and growth. Members considered that it may be appropriate to suggest a cardiac catheter if treatment is intended to be continued beyond one year.

1.26 The Subcommittee considered that, although current application numbers for patients in this category are low, there may be a larger group that could seek treatment with sildenafil. Members considered that if applications show clear evidence of PAH from birth, these patients could meet the current criteria for treatment under the classification of PPHN.

1.27 The Subcommittee considered that it may be difficult to objectify which patients should receive treatment, noting that treatment would not be required in all infants with CLD. Members considered that identifying the more severe patients that should be treated and the least severe patients who should not be treated would be straightforward, but that there would be difficulties determining whether those patients in the middle of the spectrum should be treated.

1.28 The Subcommittee considered that applications for patients with PAH secondary to CLD should include an inpatient management summary, admission history, narrative, discharge plan short and long term, including weaning plan. The Subcommittee considered that an echocardiogram should be provided.

1.29 Members considered the majority of patients born with CLD each year would do well and would not require vasodilator therapy and that 20 to 30 patients may require treatment.

1.30 The Subcommittee considered that the dose of sildenafil required for patients in this group would be 3 to 8 mg/kg/day, and that the average weight of patients would be three to five kilograms. Members considered that treatment would likely be required for up to six months post-discharge in the majority of patients, but noted that some patients may require treatment beyond six months.

1.31 The Subcommittee considered that there is no alternative treatment to sildenafil and that the use of sildenafil would result in earlier discharge from hospital and also reduce mortality and morbidity. The Subcommittee also considered that sildenafil is likely to be cost saving when compared to ongoing hospitalisation and transfers between neonatal units.

1.32 The Subcommittee considered that requests for other treatments such as iloprost or bosentan would be unlikely in this patient group.

1.33 Members **recommended** that sildenafil be funded for neonatal/infantile PAH secondary to CLD with a medium priority.

2 Patients requiring vasodilator therapy post-Fontan repair

2.1 The Subcommittee noted that in patients with a Fontan circulation, blood flow through the pulmonary vasculature is non-pulsatile. Cardiac output is dependant on pulmonary vascular resistance (PVR) and the efficiency of the circuit is reliant on PVR being low.

2.2 The Subcommittee considered that perioperative mortality is increased in patients undergoing a Fontan procedure with a raised PVR. Members noted that the availability of vasodilators means that some patients who may have previously been considered too high a risk for surgery due to their raised PVR could now be considered for surgery.

2.3 The Subcommittee considered that a good outcome from a Fontan procedure without a fenestration would be oxygen saturations around 87% to 91% and a low PVR, ideally less than 2.0 (indexed pulmonary vascular resistance) and mean pulmonary artery pressures of around 10 mmHg. Members noted that some patients may require a Fontan revision procedure at a later time. The Subcommittee considered that complications of

raised central venous pressure resulting from a Fontan procedure such as protein losing enteropathy and plastic bronchitis are rare.

2.4 The Subcommittee considered that any criteria relating to sildenafil treatment in patients with a Fontan circulation should be non-prescriptive, but considered that cardiac catheter data would be required in these patients. Criteria could include patients with complications of a Fontan circulation in the context of raised pulmonary vascular resistance or a reduced cardiac index.

2.5 The Subcommittee considered that the likely number of patients that would require treatment would be less than ten, representing two thirds of the total number of patients undergoing a Fontan procedure each year.

2.6 The Subcommittee considered that there would likely be two groups of patients that could be considered for treatment, one being those who would require treatment in the perioperative setting and another group with poor haemodynamics that may require treatment in the longer term.

2.7 Members considered that there would be about six patients per year in the perioperative group, that the average weight of these patients would be 10 to 15 kg and treatment would generally be required for less than six months at a dose of 3 to 4 mg/kg/day. The Subcommittee considered that there would be about four patients per year in the group with poor haemodynamics, that the average weight of these patients would be 15 to 20 kilograms and treatment could be required for five years or more at a dose of 3 to 4 mg/kg/day. The Subcommittee considered that the maximum dose of sildenafil required would be about 50 mg tds.

2.8 The Subcommittee considered that bosentan could be considered as an alternative treatment for these patients, although, members considered that as these patients may have hepatic congestion, care would need to be taken if bosentan was used.

2.9 The Subcommittee considered that the use of sildenafil would reduce hospitalisations and mortality and morbidity. Members considered that treatment with sildenafil resulted in patients in the group with poor haemodynamics surviving beyond five years then the use of sildenafil would be very cost-effective.

2.10 Members **recommended** that sildenafil be funded for Fontan patients with a high priority.