Pulmonary Arterial Hypertension Subcommittee of PTAC

teleconference held 4 December 2012

(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 generally 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 14 & 15 February 2013, the record of which will be made available in April 2013.

Some material has been withheld, in accordance with the Official Information Act 1982 (OIA) to:

(i) enable PHARMAC to protect the privacy of natural persons, including that of deceased natural persons (section 9(2)(a)).

1 The long-term use of sildenafil in the treatment of children

Application

1.1 The Pulmonary Arterial Hypertension Subcommittee reviewed a letter from a clinician regarding concerns with the long-term use of sildenafil in the treatment of children.

1.2 [withheld under s (9(2)(a) of the OIA

1.2.1 withheld under s (9(2)(a) of the OIA

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Recommendation

1.3 The Subcommittee recommended that:

1.3.1 The endothelin receptor antagonists (bosentan and ambrisentan) are the funded first-line treatment for children with diseases included in the STARTS-2 trial (idiopathic pulmonary arterial hypertension and pulmonary hypertension secondary to congenital heart disease) requiring long-term therapy.

1.3.2 It would be inappropriate to switch children with disease requiring long-term therapy who are currently on sildenafil to bosentan but that this could be considered by the clinicians and patients when a renewal is required or if the patient currently has a lifetime sildenafil approval.

1.3.3 Sildenafil should remain the first-line funded treatment for children with disease requiring short-term therapy and in diseases where there is no evidence or clinical experience with the use of endothelin receptor antagonists (e.g. Fontan circuits, congenital diaphragmatic hernias, persistent pulmonary hypertension of the newborn).

1.3.4 PHARMAC write to clinicians informing them of the relevant clinical information regarding the long-term use of sildenafil in children and any changes to the funding of sildenafil and endothelin receptor antagonists.

1.3.5 These minutes should be considered at the next PTAC meeting (February 2013).

The Decision Criteria particularly relevant to this recommendation are: *(iv) The clinical benefits and risks of pharmaceuticals.*

Discussion

1.4 The Subcommittee reviewed a letter from Clare O'Donnell regarding concerns with the long-term safety and efficacy of sildenafil in children with PAH as a result of the findings of the STARTS-1 and STARTS-2 trials and the recent FDA recommendation.

1.5 The Subcommittee noted that currently the first-line PAH treatment is sildenafil with bosentan being the second-line treatment. The Subcommittee noted that while the Revatio brand of sildenafil is not funded other brands of sildenafil are. The Subcommittee also noted that the cost of sildenafil is significantly lower than the cost of ERA therapy.

1.6 The Subcommittee noted that on the 30 August 2012 the FDA issued a recommendation that Revatio (sildenafil) is not prescribed to children (ages 1 to 17) for pulmonary arterial hypertension. The Subcommittee noted that this recommendation was based on the Barst et al trial ("A randomised, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naïve children with pulmonary arterial hypertension. Circulation 2012; 125:324-334) showing that children taking high dose Revatio had a higher risk of death than children taking low dose Revatio and that the low doses are not effective in improving exercise ability.

1.7 The Subcommittee noted that a letter from Pfizer to Australian clinicians noted that in the context of Studies A1481156 and A1481131 (STARTS-1 and 2) that the high dose of sildenafil was associated with a harmful effect on survival when compared to the low dose, and due to concern regarding a potential dose response relationship between increased dose and mortality it had been recommended that 40 mg and 80 mg TID doses are discontinued as well as the 20 mg TID dose in children with a body weight ≤ 20 kg. The Subcommittee noted that of the doses investigated this left the 10 mg and 20 mg TID doses for children with a body weight of >20 kg and the 10 mg dose for children with a body weight ≤ 20 kg.

1.8 The Subcommittee noted the Barst et al trial (2012 above) a randomised, double-blind, placebo-controlled, dose-ranging clinical trial of oral sildenafil citrate in 235 treatment-naïve children weighing ≥ 8 kg and aged 1 to 17 with pulmonary arterial hypertension who were randomised to low, medium or high dose Revatio (sildenafil) administered TDS or placebo for 16 weeks (STARTS-1). The Subcommittee noted that Revatio did not result in a statistically significant improvement from baseline for peak oxygen consumption for the 3 doses combined versus placebo after 16 weeks in the 115 children who were able to exercise reliably, but resulted in statistically significant improvements versus placebo for the medium dose group (PVRI) and for the high dose group (mean PAP, PVRI, Cardiac index) with the low dose group showing no statistically significant improvements (mean PAP, PVRI, Cardiac index, mean RAP, exercise duration).

1.9 The Subcommittee noted that following the 16 week period the patients were eligible to enter the long-term extension study (STARTS-2) with the placebo patients being re-randomised to one of the three dosing options (low, medium or high) and that during the long-term extension study dose titration was permitted as clinically indicated. The Subcommittee noted that the incidence of death was 9% (5 of 55), 14% (10 of 74) and 20% (20 of 100) for the low, medium and high dose groups and Kaplan-Meier survival estimates at 3 years from the start of sildenafil treatment were 94%, 93% and 89% for the low, medium and high dose groups. The Subcommittee noted a dose related mortality effect between the high dose and low dose with the high dose having a

significant worst outcome (hazard ratio of 3.5: p=0.0225) but no mortality effect between medium and low doses or the medium and high doses.

1.10 The Subcommittee noted that STARTS-2 did not include a placebo arm making the impact of sildenafil versus placebo difficult to determine. However the Subcommittee noted that the survival rate for paediatric patients with the use of sildenafil is higher than the historical pre-sildenafil survival rate as noted in the Barst et al trial (2012 above).

1.11 The Subcommittee considered that the STARTS trials indicated that high dose sildenafil resulted in increased mortality, that while there was no significant effect for medium dose sildenafil on mortality the data raised the concern that there could be an effect especially in the longer term, and that low dose sildenafil is ineffective as it did not result in any statistically significant improvements versus placebo.

1.12 The Subcommittee considered that the alternative to sildenafil is the use of bosentan. The Subcommittee noted that there are no studies comparing the two products making any comparison difficult due to a lack of appropriate data. However, the Subcommittee noted that the survival rate for paediatric patients with the use of bosentan are higher than the historical survival rates and that bosentan is the “standard of care” internationally and has been used for a number of years in the paediatric population without the appearance of any safety signals.

1.13 The Subcommittee considered that there would only be a small number of children requiring bosentan therapy for idiopathic pulmonary arterial hypertension and pulmonary hypertension secondary to congenital heart disease.