PUBLIC SUMMARY DOCUMENT
Product: Bosentan monohydrate, tablets, 62.5 mg and 125 mg (base), Tracleer®
Sponsor: Actelion Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: March 2008

1. Purpose of Application

The application sought an extension to the current Section 100 (Highly Specialised Drug) Public and Private Hospital Authority required listing to include treatment of pulmonary arterial hypertension (PAH) associated with congenital systemic to pulmonary shunts including Eisenmenger's physiology.

The application also sought to re-word the current Section 100 (Highly Specialised Drug) Public and Private Hospital Authority required listing to reflect the current clinical classification of PAH.

Highly specialised drugs are medicines for the treatment of chronic conditions, which, because or their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

At the December 2003 meeting, the PBAC recommended listing for treatment of primary pulmonary arterial hypertension or pulmonary arterial hypertension associated with scleroderma based on an acceptable, but high, cost-effectiveness ratio.

3. Registration Status

Bosentan was registered by the TGA on 20 November 2002 and is indicated for the treatment of:

- Idiopathic pulmonary arterial hypertension.
- Familial pulmonary arterial hypertension.
- Pulmonary arterial hypertension associated with scleroderma.
- Pulmonary arterial hypertension associated with congenital systemic to pulmonary shunts including Eisenmenger's physiology; in patients with WHO functional class III or IV symptoms.

4. Listing Requested and PBAC's View

Add to current listing

- Pulmonary arterial hypertension associated with congenital systemic to pulmonary shunts including Eisenmenger's physiology.

Amend current listing

Propose that primary pulmonary hypertension be re-worded for WHO Functional Class III or IV to:

- Idiopathic pulmonary arterial hypertension (iPAH)
- Familial pulmonary arterial hypertension
- Pulmonary arterial hypertension associated with scleroderma

See Recommendation and Reasons for PBAC's view

5. Clinical Place for the Proposed Therapy

Congenital heart disease (CHD) is the most common of the major congenital malformations occurring in about 5 to 8 cases per 1000 births. Ventricular septal defects (VSDs) are most frequent, followed by atrial septal defects (ASDs) and patent ductus arteriosus (PDA). If the defect is large and left-to-right (LR) shunting is chronic; exposure of the pulmonary vasculature to high systemic arterial pressure with increased blood flow levels and shear stress will lead to progressive pulmonary vascular injury and consequently increased pulmonary vascular resistance (PVR) and pulmonary arterial hypertension.

Primary, or unexplained, pulmonary arterial hypertension (PAH) is a recognised complication of congenital cardiac shunts. In Eisenmenger's physiology, initially there is a left to right shunt which over time increases pressure in the pulmonary vasculature causing pulmonary hypertension and reversal of the shunt to a right to left shunt with subsequent deoxygenated blood supplied to the systemic circulation and organs. The natural history of PAH is usually progressive, intractable and often fatal, with treatment options aimed at relieving symptoms of the disease and returning the patient to a more functional lifestyle.

Bosentan would provide a further treatment option for Class III or IV patients who do not respond to standard therapy.

6. Comparator

The submission nominated standard care as the main comparator. Standard care may include the use of supplemental oxygen, digitalis, diuretics, vasodilators, anticoagulants, or lung transplantation and repair.

7. Clinical Trials

The submission presented one randomised trial (BREATHE-5) comparing bosentan (62.5 mg for 4 weeks, and 125 mg thereafter) with placebo (standard therapy) in patients with WHO Functional Class III Eisenmenger's physiology and 11 supplementary observations (7 open-label studies, and 4 retrospective reviews) of bosentan in patient populations with PAH associated with congenital heart disease/Eisenmenger's Associated Pulmonary Arterial Hypertension – Congenital Heart Disease (APAH-CHD), NYHA/WHO Function Class (II-IV), and duration of follow-up (12 weeks to 29 months).

Randomised trials presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
BREATHE-5 (AC-052-405)	BREATHE-5: A Multi-Centre, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of Tracleer (Bosentan) on Oxygen Saturation and Cardiac Haemodynamics in Patients With Pulmonary Arterial Hypertension Related to Eisenmenger Physiology 2005, Actelion	Galie et al. (2006) Bosentan therapy in patients with Eisenmenger syndrome: A multicenter, double-blind, randomized, placebo-controlled study. *Circulation*, 114(1):48-54.

Eleven non-randomised studies were identified from external and internal (including TGA dossier) searches, and provided as supplementary evidence in the submission. These studies are listed in the table below.

Non-randomised studies presented in the submission

Trial identifier	Title and Source	Study Design
AC-052-405 (OL) 2005 [a]	A Multi-Center, Open-Label Extension Study to Protocol AC-052-405 to Evaluate the Safety and Efficacy of Tracleer (bosentan) in Patients With Pulmonary Arterial Hypertension Related to Eisenmenger Physiology	MC OL Ext
AC-052-403 2005 Ibrahim *et al.* 2006	Open-label study to investigate the safety and efficacy of Tracleer (bosentan) in adult patients with pulmonary arterial hypertension related to Eisenmenger. Allschwil, CH. Actelion Pharmaceuticals "An open-label, multicentre pilot study of bosentan in pulmonary arterial hypertension related to congenital heart disease." Canadian Respiratory Journal 13(8): 415-420	MC OL SA 16 weeks
Apostolopoulou *et al.* 2005	"Effect of the oral endothelin antagonist bosentan on the clinical, exercise, and haemodynamic status of patients with pulmonary arterial hypertension related to congenital heart disease." *Heart* **91**(11): 1447-1452	P NR OL 16 weeks
Apostolopoulou *et al.* 2007	"Long-term oral bosentan treatment in patients with pulmonary arterial hypertension related to congenital heart disease: a 2-year study." *Heart* **93**(3): 350-4	Ext of Apostolopoulou *et al.* (2005) 2 year
Christensen *et al.* 2004	"Initial experience with Bosentan therapy in patients with the Eisenmenger syndrome." American Journal of Cardiology 94(2): 261-263	
Gatzoulis *et al.* 2005	"Safety and tolerability of bosentan in adults with Eisenmenger physiology." *International Journal of Cardiology* **98**(1): 147-151	OL SA pilot 3 month
Kotlyar *et al.* 2006	"Bosentan for the treatment of pulmonary arterial hypertension associated with congenital cardiac disease." Cardiology in the Young 16(3): 268-274	Ret Review of Pts on SAC
Schulze-Neick *et al.* 2005	"Adult patients with congenital heart disease and pulmonary arterial hypertension: First open prospective multicenter study of bosentan therapy." *American Heart Journal* **150**(4): 716.e7-716.e12	Obs, OL, MC P
Sitbon *et al.* 2006	"Bosentan for the treatment of pulmonary arterial hypertension associated with congenital heart defects." European Journal of Clinical Investigation 36(SUPPL. 3): 25-31	Ret
D'Alto *et al.* 2007	"Long term effects of bosentan treatment in adult patients with pulmonary arterial hypertension related to congenital heart disease (Eisenmenger physiology): safety, tolerability, clinical, and haemodynamic effect." Heart 93(5): 621-5	OL P SA
Diller *et al.* 2007	"Long-term safety, tolerability and efficacy of bosentan in adults with pulmonary arterial hypertension associated with congenital heart disease." Heart 93(8): 974-6	Ret

Abbreviations: OL=open label; Obs=observational; MC=multicentre; P=prospective; Ret=retrospective; NR=non randomised; SA=single arm; U=uncontrolled; Ext=extension; SAC=special access scheme for bosentan; Pts=patients; a=Open-label extension study to BREATHE-5.

8. Results of Trials

Bosentan significantly improved indexed pulmonary vascular resistance (PVRi) compared to placebo in Eisenmenger's patients. No negative effects on haemodynamic measures or

oxygen saturation were observed. Functional improvement was associated with a +53 m (placebo-corrected) improvement in the six-minute walk test (6MWT). WHO Functional Class improved in 35% and 13% of bosentan treated and placebo patients, respectively.

The results from BREATHE-5 are presented below:

BREATHE-5: Primary outcome: Change from baseline to Week 16 in mean oxygen saturation at rest with room air (per protocol analysis)

O2 saturation at rest with room air	**Bosentan**	**Placebo**
n [a]	35	17
Baseline (mean±sd)	82.4±5.3%	83.6±5.1%
Week 16(mean±sd)	83.8±5.5	84±6.7
Change from baseline (mean±sd)	1.5±2.5	0.4±3.7
Treatment effect (mean±sd)	1±3.0	
95%CI	-0.7, 2.8	
PVRi [c]		
n [b]	36 [d e]	17 [d]
Baseline (mean±sd)	3425.1±1410.5	2870.0±1209.3
Week 16(mean±sd)	3108.2±1342.1	3025.1±1230.0
Change from baseline (mean±sd)	-316.9±830.1	155.1±552.7
Treatment effect (mean±sd)	-472.0±754.1	
95%CI	-917.6, -26.5	
p-value (t-test)	p=0.0383	

Note: Missing values at week 16 substituted as per SAP rules.
a=per protocol analysis; b=all randomised analysis; c= PVRi was analysed per country. The results did not identify any specific outliers; d=Two bosentan-treated patients and 2 placebo-treated patients had no post-treatment PVRi assessment, and assigned 'worst rank value' (baseline value corrected with the highest percentage of worsening from baseline observed during the study on the patient set under analysis);
e=A bosentan-treated patient was excluded from the analysis because the catheterization time window was outside the allowed range at screening.

BREATHE-5 Secondary outcome

6MWTdistance	**Placebo**	**Bosentan**
Baseline (mean±sd)	366.4±16.4 m	331.9±13.6 m
Wk 16 change from baseline (mean±sd)	-9.7 ± 22.3 m	+43.4 ± 8.1 m
Treatment effect (mean±sd)	*+53.1 ± 19.2 m*	
p-value (t-test)	*p = 0.0079*	

The direction of findings presented as supplementary evidence are consistent with pivotal trial results, however, the PBAC considered that the strength of reported outcomes and between-study comparative value should be interpreted cautiously in view of their observational nature.

The PBAC also considered that the data in support of the younger paediatric patients, or WHO Functional Class IV symptom severity are either not available or are weak but noted that high quality evidence is difficult to obtain in these populations.

The toxicity profile of bosentan in Eisenmenger's appears consistent with iPAH and Systemic Sclerosis (APAH-SSc). The periodic safety update report did not identify any unexpected adverse events.

9. Clinical Claim

The submission described bosentan as equivalent in terms of comparative effectiveness and comparative safety in APAH-CHD to other PBS-listed PAH aetiology groups.

10. Economic Analysis

An economic evaluation for bosentan in APAH-CHD was not presented. The reason provided for this omission was that the cost effectiveness of bosentan in APAH-CHD is likely to be similar to that previously demonstrated for iPAH.

The PBAC previously accepted an economic model (2002) estimating the cost-effectiveness of bosentan in iPAH. The cost effectiveness of bosentan in Eisenmenger's patients was considered to be similar to that previously demonstrated for iPAH. This published model was used in the current submission for the new indication (APAH-CHD). The original model presented for iPAH estimated the incremental cost effectiveness ratio at 15 years in the range of $45,000 to $75,000 per year of life (without continuation rules, or lower but within the same range after continuation rules were added). The PBAC noted the population in the model was not the population for whom the current submission was sought.

The PBAC considered the pathophysiology of APAH-CHD was no different to iPAH and that this condition should respond to the same drugs as iPAH.

11. Estimated PBS Usage and Financial Implications

The submission estimated the number of patients per year to be less than 10,000 in Year 5 at an estimated financial cost per year to the PBS of less than $10 million in Year 5.

The PBAC noted the sponsor has previously entered into a confidential Special Pricing Arrangement that allows a rebate to the PBS from the first day of listing.

12. Recommendation and Reasons

The PBAC recommended the listing of bosentan on the PBS for the treatment of pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts including Eisenmenger's physiology (APAH-CHD) based on acceptable cost-effectiveness compared with standard care.

The PBAC accepted the assumption that APAH-CHD patients are similar to idiopathic pulmonary arterial hypertension (iPAH) patients and that the cost effectiveness of bosentan in Eisenmenger's patients is similar to that demonstrated for iPAH, which was accepted by the PBAC in 2002, with the original model being the one used in this submission for the new indication. This original model estimated the ICER for iPAH at 15 years as between $45,000 and $75,000 (without continuation rules, or lower, but within the same range after continuation rules were added). The PBAC considered that the pathophysiology of APAH-CHD was essentially similar to iPAH and that this condition should respond to the same drugs as iPAH.

The PBAC noted that the previous submissions for bosentan used the 6 minute walk test (6MWT) as the most widely accepted surrogate clinical outcome. The FDA now mandates this test as the surrogate outcome for all drugs used to treat PAH and the PBAC has previously accepted the 6MWT as an appropriate surrogate outcome. In addition, insertion of a right heart catheter carries a significant risk of serious complications and even death in some paediatric patients, as a general anaesthetic has to be administered. However, the PBAC noted that no statistical comparisons are presented on the intermediate outcomes of 6MWT and WHO Functional Class and that the results are not comparable due to trial design, population and disease characteristics.

The PBAC considered that the data in support of the younger paediatric patients, or WHO Functional Class IV symptom severity are either not available or are weak but noted that high quality evidence is difficult to obtain in these populations. Therefore, WHO functional class IV patients should be included in the restriction and children should not be specifically excluded. The PBAC considered that the estimates of patient numbers used in the financial implications are also uncertain.

The PBAC decided not to change the wording of the restrictions for bosentan and other drugs used for PAH WHO functional Class III and IV, consistent with discussions from the 26 February 2008 PAH meeting with sponsors and clinicians, as new Consensus Guidelines, which will produce significant changes to the current guidelines, will be published later this year following an International meeting. Further discussion will be needed with the Thoracic Society regarding the implications of these changes for the drugs listed on the PBS for PAH.

The PBAC noted advice from the Highly Specialised Drugs Working Party, which supported the inclusion of bosentan under the HSD program.

Recommendation
BOSENTAN MONOHYDRATE, tablets, 62.5 mg (base) and 125 mg (base),

Restriction: **To be finalised**
Public and private hospital authority required

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor welcomes the PBAC's recommendation for the listing of bosentan (Tracleer) for the treatment of pulmonary arterial hypertension associated with congenital systemic to pulmonary shunts including Eisenmenger's physiology, as it provides an important therapy for the treatment of this rare and severe condition.