PUBLIC SUMMARY DOCUMENT

Product: MACITENTAN, tablet, 10mg, Opsumit®
Sponsor: Actelion Pharmaceuticals Australia Pty Ltd.
Date of PBAC Consideration: March 2014

1. Purpose of Application

To request a Section 100 (Highly Specialised Drugs Program) listing for macitentan to treat idiopathic pulmonary arterial hypertension (IPAH), PAH secondary to connective tissue disease (PAH-CTD) and PAH associated with congenital heart disease (PAH-CHD) in patients with WHO Functional Class (FC) III and IV severity.

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

2. Background

The submission was made under the TGA/PBAC Parallel Process, however macitentan was TGA registered at the time of the PBAC meeting.

This drug had not been previously considered by the PBAC.

3. Registration Status

Macitentan was listed on the Australian Register of Therapeutic Goods on 5 February 2014.

Macitentan, as monotherapy or in combination with approved PAH treatments (phosphodiesterase-5 inhibitors or inhaled prostanoids), is indicated for the treatment of:

- idiopathic pulmonary arterial hypertension
- heritable pulmonary arterial hypertension
- pulmonary arterial hypertension associated with connective tissue disease
- pulmonary arterial hypertension associated with congenital heart disease with repaired shunts
- in patients with WHO Functional class II, III or IV symptoms.

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drugs)
(Public and Private Hospital Authority Required)
Initial treatment (new patients):
Patients who have not received prior PBS-subsidised treatment with a PAH agent and who have WHO FC III or IV idiopathic PAH (IPAH), PAH secondary to connective tissue disease (PAH-CTD); or PAH associated with a congenital systemic-to-pulmonary shunt (including Eisenmenger's physiology) (PAH-CHD)

Initial treatment (change or recommencement for all patients):

Patients with IPAH, PAH-CTD or PAH-CHD who wish to recommence after a break and have previously responded to macitentan, or who wish to switch to macitentan from an alternate PAH agent;

Continuing treatment (all patients):
Patients who have received approval for initial PBS-subsidised treatment with macitentan and who have achieved a response to their most recent course of macitentan treatment; and

Cessation of treatment (all patients):
Patients with WHO FC III or IV IPAH, PAH-CTD or PAH-CHD who have not responded to macitentan.

The submission presented a cost minimisation analysis, compared to bosentan. The submission proposed the same restriction as that for bosentan, which the PBAC considered appropriate.

5. Clinical Place for the Proposed Therapy

PAH is a serious and progressive disorder that results in right ventricular dysfunction and impairment in activity tolerance. If not treated, it can lead to heart failure and death. There is currently no cure for PAH other than lung transplantation.

Macitentan is an alternative oral endothelin receptor antagonist (ERA) treatment option. Currently ambrisentan and bosentan are the only other ERAs listed on the PBS. Other PBS-listed agents used to treat PAH are phosphodiesterase type 5 (PDE5) inhibitors (sildenafil and tadalafil) and vasodilators (epoprostenol and iloprost).

6. Comparator

The submission nominated bosentan as the comparator. The PBAC considered this to be appropriate.

7. Clinical Trials

No head-to-head randomised controlled trials (RCTs) of macitentan and bosentan were identified. The submission was based on the indirect comparison between:

- One macitentan RCT (SERAPHIN) comparing macitentan 10mg once daily with placebo; and
- Four bosentan trials comparing bosentan at an initiation dose of 62.5mg twice a day for 4 weeks, followed by a dose of 125mg twice a day, with placebo (Study 351, BREATHE-1, EARLY and STRIDE-2).

The table below summarises the trials included in the indirect comparison:

Trials presented in the submission for the indirect comparison

Trial	Description	Reports
Common reference: placebo *Macitentan*		
SERAPHIN	Multi-centre RCT in patients with WHO FC II-IV IPAH, PAH-CTD, PAH-CHD, PAH-HIV	AC-055-302 SERAPHIN: Study with endothelin receptor antagonist in pulmonary arterial hypertension to improve clinical outcome: a

	or PAH due to drugs and toxins	multicenter, double-blind, randomized, placebo-controlled, parallel-group, event-driven, phase III study to assess the effects of macitentan on morbidity and mortality in patients with symptomatic pulmonary arterial hypertension. 2012 Pulido T, Adzerikho I, Channick RN, *et al.* Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension. *New England Journal of Medicine* 2013; 369 (9):809-818.
Bosentan		
Study 351	RCT in treatment naïve patients with WHO FC III-IV IPAH or PAH-CTD	AC-052-351 Final study report: A pilot double-blind, randomized, placebo-controlled study to assess the effects of Ro 47-0203 (bosentan) on exercise capacity, hemodynamics, and quality of life of patients with primary pulmonary hypertension or pulmonary hypertension due to scleroderma. Study No. 2000 AC-052-353 Final Study Report: Open label long term study in patients with pulmonary arterial hypertension who participated in controlled clinical studies with bosentan. 2004 Channick, RN, Simonneau G, Sitbon O, *et* al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001; 358(9288): 1119-1123. BadeschDB, Bodin F, Channick RN, *et* al. Complete results of the first randomized, placebo-controlled study of bosentan, a dual endothelin receptor antagonist, in pulmonary arterial hypertension. *Current Therapeutic Research - Clinical and Experimental* 2002; 63(4): 227-246
BREATHE-1	RCT in treatment naïve patients with WHO FC III-IV IPAH or PAH-CTD	AC-052-352 Final study report: A double-blind, randomized, placebo-controlled study to assess the effects of Ro 47-0203 (bosentan) on exercise capacity in patients with pulmonary arterial hypertension. 2001 AC-052-354 Final Study Report: Long term open label study in patients with pulmonary hypertension who participated in controlled clinical studies with bosentan. 2004 Rubin, LJ, Badesch DB, Barst RJ, *et al*. Bosentan therapy for pulmonary arterial hypertension. *New England Journal of Medicine* 2002; 346(12): 896-903 Galiè N, Hinderliter AL, Torbicki A, *et al*. Effects of the oral endothelin-receptor antagonist bosentan on echocardiographic and doppler measures in patients with pulmonary arterial hypertension. *Journal of the American College of Cardiology* 2003; 41(8): 1380-1386
EARLY	RCT in patients with WHO FC II IPAH, PAH-CTD, PAH-CHD, PAH-HIV or PAH due to anorexigens	AC-052-364 Final study report on the double-blind period: A randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy, safety, and tolerability of bosentan in patients with mildly symptomatic pulmonary arterial hypertension (EARLY). 2007 Galiè, N, Rubin L, Hoeper M, *et al*. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008; 371(9630): 2093-2100.
STRIDE-2	RCT in treatment naïve patients with WHO FC II-IV IPAH, PAH-CTD or PAH-CHD	Barst, RJ, Langleben, D, Badesch, D, *et al.* Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxentan. *Journal of the American College of Cardiology*

		2006; 47(10): 2049-2056.

RCT = randomised controlled trial; FC = Functional Class; PAH = pulmonary arterial hypertension; IPAH = idiopathic PAH; CTD = connective tissue disease; CHD = congenital heart disease; HIV = human immunodeficiency virus infection

The PBAC noted there were no consumer comments for this item.

The PBAC noted that the sponsor did not request a hearing for this item.

8. Results of Trials

No minimum clinically important difference (MCID) was specified in the submission. Non-inferiority limits of -35m and -50m in 6-minute walk distance (6MWD) had previously been accepted by the PBAC.

In SERAPHIN, changes in 6MWD from baseline were measured at Month 6, rather than at the end of the treatment (median: 115 weeks). In the table below, the whole confidence interval (CI) in the indirect comparison of the difference in 6MWD is above a non-inferiority limit of -35m. However, there were differences between the macitentan and bosentan trials in patient characteristics (e.g. PAH aetiology, WHO FC severity and concomitant PAH treatment), durations of treatment, time points for measurement of outcomes, definitions of outcomes, and methods of statistical analysis. In addition, 82.6% of patients in SERAPHIN, all participants in EARLY and about one-third of patients in STRIDE-2 (36.9%) were not consistent with the requested PBS target population, i.e. they had WHO FC II severity and/or had stable PAH but receiving add-on treatment with another PAH agent.

Results of mean change in 6MWD from baseline[a] – Overall population

Trial ID	Trial of macitentan			Trials of bosentan			Indirect comparison[e] Absolute difference (m) [95% CI]
	Absolute difference (m)[b] [95% CI]	Macitentan *N* Mean (SD)[c]	Placebo N Mean (SD)[c]	Placebo N Mean (SD)[c]	Bosentan *N* Mean (SD)[c]	Absolute difference (m)[d] [95% CI]	
SERAPHIN	21.9 [5.5, 38.3]	N=242 12.5 (83.5)	N=250 -9.4 (110.6)	–	–	–	-7.2 [-29.4, 15.1]
Study 351	–	–	–	N=11 -5.8 (120.5)	N=21 70.1 (56.2)	76.0 [14.9, 137.2]	
BREATHE-1	–	–	–	N=69 -7.8 (96.1)	N=74 26.8 (75.3)	34.6 [6.4, 62.8]	
EARLY	–	–	–	N=92 -7.9 (78.9)	N=93 11.2 (73.8)	19.1 [-1.9, 40.1]	
STRIDE-2	–	–	–	N=62 NR	N=60 NR	29.5 [0.3, 58.7]	
Pooled absolute difference[f] (m) [95% CI]	–	–	–	29.1 [14.0, 44.2] *Test of heterogeneity: χ^2: 3.27, df: 3, p-value: 0.351*			

6MWD = 6-minute walk distance; CI = confidence interval; NR = not reported

[a] Time points: 6 months in SERAPHIN; 12 weeks in Study 351; 16 weeks in BREATHE-1; 6 months in EARLY; and 18 weeks in STRIDE-2.

[b] Macitentan *vs* placebo. A positive result indicates treatment effect favouring macitentan.

[c] *SDs have been extracted from relevant clinical study reports.*

[d] Bosentan *vs* placebo. A positive result indicates treatment effect favouring bosentan.

[e] Macitentan *vs* bosentan. A negative result indicates treatment effect favouring bosentan.

[f] Pooled using random effects model. *Test of heterogeneity was conducted during the evaluation.*

In the indirect comparison targeting the WHO FC III/IV treatment naïve subgroup, the lower bound of the CI of the difference in 6MWD was outside -35m and -50m, indicating that macitentan may be inferior to bosentan in the PBS target population. The PBAC considered

that these results may have been affected by the different imputation methods used across the trials, along with the exchangeability concerns mentioned above.

Long-term results from SERAPHIN showed that macitentan was superior to placebo in delaying the first morbidity/mortality event. However, no comparable data were available for bosentan to enable a meaningful indirect comparison in terms of this endpoint. The PBAC considered the time to first mortality/morbidity event a more patient relevant outcome than the 6MWD.

A summary of the primary composite endpoint of mortality/morbidity reported in SERAPHIN is presented in the table below. The PBAC noted that survival data for each component of the primary endpoint were not available.

Morbidity/mortality events in SERAPHIN

	n (%)		HR [95% CI]	Absolute risk difference [95% CI]	Relative risk [95% CI]
	Macitentan (N=242)	Placebo (N=250)			
Morbidity/mortality event	76 (31.4%)	116 (46.4%)	0.55 [0.32, 0.76]	-15.0% [-23.5%, -6.5%]	0.68 [0.54, 0.85]
– Worsening of PAH	59 (24.4%)	93 (37.2%)	–	-12.8% [-20.9%, -4.8%]	0.66 [0.50, 0.86]
– Death	16 (6.6%)	17 (6.8%)	–	-0.2% [-4.6%, 4.2%]	0.97 [0.50, 1.88]
– Prostanoid initiation	1 (0.4%)	6 (2.4%)	–	-2.0% [-4.1%, 0.1%]	0.17 [0.02, 1.42]

PAH = pulmonary arterial hypertension; HR = hazard ratio; CI = confidence interval
Source: Pulido *et al* 2013

The PBAC noted the exchangeability concerns relating to the indirect analysis, but considered that on balance the evidence provided in the submission supported the claim of non-inferiority.

The PBAC noted that the safety data presented in the submission had limitations, given the exchangeability concerns, the short study periods (especially in the bosentan trials), and the small sample sizes of the clinical trials in the evidence base.

Reduced haemoglobin levels and anaemia are known adverse events (AEs) associated with treatment with the ERA drug class. In SERAPHIN, haemoglobin decreased in 15.7% of patients receiving macitentan compared to 4.8% receiving placebo ($p < 0.001$). Anaemia rates were statistically significantly higher for patients treated with macitentan compared to placebo (13.2% vs 3.2%, $p < 0.001$). Similar results were not reported in the four bosentan trials, which could be due to the short study periods and small number of subjects in these trials. From the indirect comparison, no notable differences were observed in the safety of macitentan compared to bosentan in terms of peripheral oedema or AEs leading to discontinuation – although this comparison may have been affected by lack of exchangeability between the trials.

The rates of abnormal liver function were comparable in the two treatment arms in SERAPHIN over a treatment period of >2 years (macitentan vs placebo: 2.5% vs 3.6%). In the four bosentan trials, the proportions of patients treated with bosentan who had abnormal liver function results were slightly higher than the patients in the placebo groups (ranges:

4.1% - 11.7% vs 0% - 6.5% in placebo arms) during treatment periods of 12 weeks to 6 months. Of note, not all abnormal liver function tests reported in the clinical trials were of clinical relevance. Macitentan belongs to the ERA drug class for which hepatotoxicity is a well recognised adverse effect. The PBAC recalled in its consideration of ambrisentan (compared with bosentan via an indirect comparison), the safety results showed that bosentan increased the risk of abnormal liver function compared to placebo; whilst liver function test levels in patients treated with ambrisentan appeared unremarkable throughout a 2-year study period. The PBAC "…considered the toxicity of ambrisentan appeared non-inferior to bosentan…… the PBAC considered that additional time is required to determine whether ambrisentan is associated with liver toxicity as such adverse effects may emerge with longer term treatment" (PSD: Ambrisentan, July 2009).

With the experience of the withdrawal of sitaxentan from the market in 2010 due to concerns about liver toxicity, the PBAC considered that physicians were most likely to closely monitor the liver function of patients when prescribing new treatments for PAH. In the pre-PBAC response the sponsor claimed that macitentan is not a substrate for the bile salt export pump and therefore unlikely to be associated with hepatotoxicity.

The PBAC considered that overall macitentan was non-inferior in terms of safety when compared to bosentan. The PBAC considered it was biologically plausible that there may be reduced hepatotoxicity with macitentan (compared to bosentan), but given the absence of direct clinical evidence and longer term follow-up, no claim of superiority in terms of safety could be accepted.

9. Clinical Claim

The submission described macitentan as non-inferior in terms of comparative effectiveness, and "possibly superior" in terms of comparative safety, over bosentan.

The PBAC considered that the data supported the claim of non-inferior comparative effectiveness of macitentan over bosentan.

The PBAC did not consider the claim of "possible superiority" in terms of comparative safety was supported by the data presented in the submission. The PBAC considered that macitentan is likely non-inferior to bosentan.

10. Economic Analysis

The submission presented a cost-minimisation analysis of macitentan against bosentan. The equi-effective doses were estimated as macitentan 10mg once daily versus bosentan 62.5mg twice daily for 4 weeks, then a maintenance dose of 125mg twice daily. The submission proposed the same drug costs for macitentan and bosentan.

Other costs considered in the analysis were associated with management of adverse events (abnormal liver function), monitoring of liver aminotransferase levels and PAH-related hospitalisation costs. The submission assumed that the use of macitentan would result in a cost saving when compared with bosentan, due to the superior hepatic safety profile of macitentan over bosentan.

The PBAC considered that the comparative safety of macitentan over bosentan in terms of abnormal liver function tests is not yet established given the absence of direct clinical

evidence and longer term follow-up. The PBAC considered that the current data on safety and monitoring requirements were not sufficient to recommend adjustment based on savings or costs beyond the cost of the drug itself.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5. The submission estimated nil net financial implications to the PBS. The PBAC considered that this was reasonable.

The PBAC noted that the submission's estimate of cost savings to the MBS was based on the submission's claim of superior hepatic safety of macitentan over bosentan and considered that this had not been established.

12. PBAC Outcome

The PBAC recommended the listing of macitentan, on the basis that it should be available only under special arrangements under section 100. The PBAC recommended the special arrangements described in the recommended listing below.

The PBAC accepted that bosentan is the appropriate comparator.

Based on the data provided, the PBAC accepted that treatment with macitentan resulted in neither a statistically significant, nor clinically relevant, difference in 6MWD compared to bosentan. The PBAC considered that the data provided adequately supported the submission's claim that macitentan is non-inferior in terms of comparative effectiveness and comparative safety to bosentan.

The PBAC did not accept that macitentan was possibly superior to bosentan in terms of safety as claimed in the submission. This was due to the absence of direct clinical evidence and longer term data.

The PBAC considered that a cost-minimisation economic analysis was the appropriate approach based on the evidence presented for non-inferiority. The PBAC considered that the impact of listing macitentan should be cost neutral for the PBS.

The PBAC noted that the PBS restrictions for the pulmonary arterial hypertension (PAH) agents have not been updated for some time and note that terminology and clinical guidelines have since changed. The PBAC recommended that the restrictions for the PAH agents be reviewed to reflect current clinical guidelines on the proviso that the resultant change does not create any additional expenditure for the Commonwealth.

The PBAC recommended that the Safety Net 20 Day Rule should not apply, as it does not currently apply to Section 100 listings.

The PBAC advised the Minister that under Section 101 3BA of *National Health Act*, macitentan should be treated as interchangeable on an individual patient basis with bosentan.

Recommendation:
Add new item:

Restrictions to be finalised.

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

Actelion Pharmaceuticals welcome the decision to make Opsumit available on the PBS.