PUBLIC SUMMARY DOCUMENT
Product: Tadalafil, tablet, 20 mg, Adcirca®
Sponsor: Eli Lilly Australia Pty Ltd
Date of PBAC Consideration: November 2011

1. Purpose of Application

To request a Section 100 (Highly Specialised Drugs Program) Authority Required listing for the treatment of WHO functional class III primary pulmonary arterial hypertension (PAH) and WHO functional class III PAH secondary to connective tissue disease in a patient who meets certain criteria.

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

This drug had not previously been considered by the PBAC.

3. Registration Status

Tadalafil was registered by TGA on 10 August 2011 for the indication:

> Tadalafil is indicated in adults for the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.

4. Listing Requested and PBAC's View

Section 100 Highly Specialised Drugs Program
Public and Private Hospital Authority Required
Initial (new patients)
Application for initial PBS-subsidised treatment with tadalafil of patients who have not received prior PBS-subsidised treatment with a PAH agent and who have been assessed by a physician from a designated hospital to have:
(a) WHO Functional Class III primary pulmonary hypertension and a mean right atrial pressure of 8 mmHg or less, as measured by RHC, or, where a RHC cannot be performed on clinical grounds, right ventricular function as assessed by ECHO; OR
(b) WHO Functional Class III pulmonary arterial hypertension secondary to connective tissue disease and a mean right atrial pressure of 8 mmHg or less, as measured by RHC, or, where a RHC cannot be performed on clinical grounds, right ventricular function as assessed by ECHO.

Patients must have failed to respond [see Note for definition of response] to 6 or more weeks of appropriate vasodilator treatment unless intolerance or a contraindication to such treatment exists.

Applications for authorisation must be in writing and must include:
(1) a completed authority prescription form; and
(2) a completed Pulmonary Arterial Hypertension PBS Authority Application - Supporting Information form [www.medicareaustralia.gov.au] which includes results from the 3 tests below, where available:
(i) RHC composite assessment; and
(ii) ECHO composite assessment; and
(iii) 6MWT; and
(3) a signed patient and prescriber acknowledgment indicating that the patient understands and acknowledges that PBS-subsidised treatment with a PAH agent will cease if the treating physician determines that the patient has not achieved a response to treatment [see Note for definition of response].

Details of prior vasodilator treatment, including the dose and duration of treatment, must be provided at the time of application. Where the patient has an adverse event to a vasodilator or where vasodilator treatment is contraindicated, details on the nature of the adverse event or contraindication according to the TGA-approved Product Information must also be provided with the application.

Where fewer than 3 tests (see requirement 2 above) are able to be performed on clinical grounds, a patient specific reason outlining why the particular test/s could not be conducted must be provided with the authority application [see Note for test requirements].

The maximum quantity authorised will be limited to provide sufficient supply for 1 month of treatment, based on the dosage recommendations in the TGA-approved Product Information. A maximum of 5 repeats may be requested. Where fewer than 5 repeats are requested at the time of application, authority approvals for sufficient repeats to complete a maximum of 6 months of treatment may be requested by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Authority Required
Initial (change or re-commencement for all patients)
Application for initial PBS-subsidised treatment with tadalafil of patients with one of the following:
(a) WHO Functional Class III primary pulmonary hypertension or pulmonary arterial hypertension secondary to connective tissue disease who wish to re-commence PBS-subsidised tadalafil after a break in therapy and who have demonstrated a response to their most recent course of PBS-subsidised treatment with tadalafil; OR
(b) WHO Functional Class III primary pulmonary hypertension or pulmonary arterial hypertension secondary to connective tissue disease and whose most recent course of PBS-subsidised treatment was with a PAH agent other than tadalafil.

Applications for authorisation must be in writing and must include:
(1) a completed authority prescription form; and
(2) a completed Pulmonary Arterial Hypertension PBS Authority Application - Supporting Information form [www.medicareaustralia.gov.au] which includes the results on which approval for the first application for PBS-subsidised PAH agent was granted; and
(3) the date of the first application for PBS-subsidised treatment with a PAH agent; and
(4) the results of the patient's response to treatment with their last course of PBS-subsidised PAH agent.

Where fewer than 3 tests (see requirement 2 above) are able to be performed on clinical grounds, a patient specific reason outlining why the particular test/s could not be conducted must be provided with the authority application [see Note for test requirements].

The maximum quantity authorised will be limited to provide sufficient supply for 1 month of treatment, based on the dosage recommendations in the TGA-approved Product Information. A maximum of 5 repeats may be requested. Where fewer than 5 repeats are requested at the time of application, authority approvals for sufficient repeats to complete a maximum of 6 months of treatment may be requested by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Authority Required
Continuing treatment (all patients)
Continuing PBS-subsidised treatment with tadalafil of patients who have received approval for initial PBS-subsidised treatment with tadalafil, and who have been assessed by a physician from a designated hospital to have achieved a response to their most recent course of tadalafil treatment [see Note for definition of response].

Applications for authorisation must be in writing and must include:
(1) a completed authority prescription form; and
(2) a completed Pulmonary Arterial Hypertension PBS Authority Application - Supporting Information form [www.medicareaustralia.gov.au] which includes results from the 3 tests below, where available:
(i) RHC composite assessment; and
(ii) ECHO composite assessment; and
(iii) 6MWT.

The results of the same tests as conducted at baseline should be provided with each written continuing treatment application (i.e. every 6 months), except for patients who were able to undergo all 3 tests at baseline, and whose

subsequent ECHO and 6MWT results demonstrate disease stability or improvement, in which case RHC can be omitted. In all other patients, where the same test(s) conducted at baseline cannot be performed for assessment of response on clinical grounds, a patient specific reason why the test(s) could not be conducted must be provided with the application.

The maximum quantity authorised will be limited to provide sufficient supply for 1 month of treatment, based on the dosage recommendations in the TGA-approved Product Information. A maximum of 5 repeats may be requested. Where fewer than 5 repeats are requested at the time of application, authority approvals for sufficient repeats to complete a maximum of 6 months of treatment may be requested by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Pulmonary Arterial Hypertension (PAH) is a rare and debilitating chronic disease of the pulmonary vasculature characterised by a progressive increase in pulmonary vascular resistance that if not treated ultimately leads to right heart failure and premature death. There is currently no cure for PAH other than lung transplantation.

Patients with PAH have progressive changes to their pulmonary arteriolar vessels. The consequence of these changes is increased pulmonary vascular resistance (PVR), which increases right ventricular afterload. Patients become symptomatic mainly because the right ventricle is unable to overcome the increased afterload, and therefore cardiac output (CO) cannot increase sufficiently to match oxygen (O_2) demand. This results in the nonspecific symptoms typically observed at initial presentation, including dyspnoea during exercise, fatigue, chest pain, syncope, palpitations, and lower extremity oedema.

The submission proposed that the place in therapy of tadalafil is to provide an alternative PBS listed phosphodiesterase type-5 inhibitor (PDE5) oral treatment option for the treatment of PAH, which is given once daily.

6. Comparator

The submission nominated sildenafil as the comparator. The PBAC agreed this was appropriate.

7. Clinical Trials

The basis of the submission was an indirect comparison between tadalafil and sildenafil via placebo as the common reference.

One double-blind, randomised, controlled trial (P-HIRST) compared multiple doses of tadalafil, including 40 mg tadalafil once daily (od), with placebo over 16 weeks. A second double-blind, randomised, controlled trial (SUPER) compared multiple doses of sildenafil, including sildenafil 20 mg three times daily (tds), with placebo over 12 weeks.

More than half (53%) the patient population in P-HIRST had concomitant maintenance treatment with bosentan, whilst the eligibility criteria of SUPER did not allow concurrent use of PAH specific therapies. Therefore, the indirect comparison compared the SUPER intention-to-treat (ITT) population on sildenafil 20 mg tds and a subgroup of the P-HIRST population who were receiving 40 mg tadalafil once daily and no concomitant bosentan (which reflects the intended use of tadalafil as monotherapy).

Details of the trials published at the time of submission are in the table below.

Trials considered in the submission for the indirect comparison.

Trial ID / First author	Protocol title / Publication title	Publication citation
Common reference placebo		
Tadalafil		
P-HIRST Galie *et al*. (2009) Pepke-Zaba *et al*. (2009) Croxtal *et al*. (2010)	 Tadalafil therapy for pulmonary arterial hypertension. Tadalafil therapy and health-related quality of life in pulmonary arterial hypertension. Tadalafil: In pulmonary arterial hypertension.	 Circulation 119(22): 2894-903 Current medical research and opinion. 25(10): 2479-85 Drugs. 70 (4): 479-488
Sildenafil		
SUPER Galie *et al.* (2005b) Badesch *et al.* (2007) Pepke-Zaba (2008) Gilbert *et al*. (2009)	 Sildenafil citrate therapy for pulmonary arterial hypertension. Sildenafil for pulmonary arterial hypertension associated with connective tissue disease. Sildenafil improves health-related quality of life in patients with pulmonary arterial hypertension. Estimating a minimally important difference in pulmonary arterial hypertension following treatment with sildenafil.	 New England Journal of Medicine. 353 (20): 2148-2157. Journal of Rheumatology. 34(12): 2417-22 Chest. 133(1): 183-9 Chest. 135(1): 137-42

8. Results of Trials

The results for the indirect comparison of the primary outcome, change from baseline in 6 minute walk distance (6MWD), from the P-HIRST (patients not on bosentan) and SUPER trials are presented in the table below:

Indirect comparison of mean change from baseline in 6MWD (metres) between tadalafil and sildenafil (via placebo as the "common reference")

	P-HIRST (Subgroup: No concomitant bosentan)		SUPER (ITT)	
	Tadalafil only 40mg od	**Placebo**	**Placebo**	**Sildenafil 20mg tds**
N	37*	35	70	69
WHO FC distribution at baseline[§] WHO FC II, N (%) WHO FC III, N (%)	 9 (24) 27 (73)	 10 (27) 25 (68)	 32 (46) 34 (49)	 24 (35) 40 (58)
Mean baseline 6MWD (SD)	343 (81)	347 (76)	347 (79)	346 (90)
Mean 6MWD at end of study (Measured at Week 16 for P-HIRST and at Week 12 for SUPER).	385 (92)	344 (102)	NR	NR
Mean change from baseline, m, (SD) 95% Confidence interval	42.2 (46.5) 26.7, 57.7	-2.9 (58.1) -22.9, 17.1	-3.7 (52.8) -16.7, 9.3	41.4 (54.8) 28.0, 54.8
Difference in mean 6MWD change: Active drug-Placebo (95% CI)	45.1 (20.8, 69.3)		45.1 (26.8, 63.4)	
Indirect comparison Mean (95% CI)	-0.03 (-30.4, 30.3)			

[§]Note: Includes a WHO FC population broader than that for whom PBS listing of tadalafil is sought (WHO Class III patients)).
[*]Includes 1 patient in WHO Class I
6MWD=6minute walk distance; SD=Standard deviation; NR=Not reported in submission or published report.

The baseline mean 6MWD in the treatment arms from both trials were similar. Both active treatments resulted in a statistically significant improvement in 6MWD from baseline of approximately 40 metre gain in both trials. The mean changes in 6MWD from baseline, in the placebo arms of both trials were also similar but there was less precision in the P-HIRST placebo arm because of the smaller subgroup of patients who were not on concomitant bosentan.

The indirect comparison of 6MWD between tadalafil (no bosentan use) and sildenafil, via placebo as the common reference, showed a non-statistically significant difference in means: 0.03 metres (95% CI: -30.4, 30.3).

Indirect comparison analyses for improvement in functional status, clinical worsening and haemodynamic parameters also suggested no statistically significant differences between tadalafil and sildenafil.

For PBAC's view of these results, see Recommendation and Reasons.

The most common adverse event in the active treatment arms was headache. Diarrhoea, dyspepsia and nausea were more common with sildenafil, although the placebo rates in the SUPER trial were greater than the placebo rates in the P-HIRST trial. Myalgia and back pain were similar in both active treatment arms.

No new safety issues were identified beyond those observed in the key P-HIRST trial.

The comparative safety of tadalafil and sildenafil remains uncertain given that there are no head-to-head or long term safety data available.

9. Clinical Claim

The submission described tadalafil as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over sildenafil.

The PBAC considered that although the quality of data is poor, it is probably reasonable to accept that tadalafil is non-inferior to sildenafil in terms of comparative effectiveness and safety.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses, as described in the submission, are tadalafil 40 mg (2 × 20 mg od) = sildenafil 60 mg (20 mg tds).

11. Estimated PBS Usage and Financial Implications

The likely number of patients treated was estimated by the submission to be less than 10,000 over the first 5 years. The estimate is uncertain.

The net financial cost to the PBS was estimated by the submission to be less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended listing tadalafil on the PBS in the Section 100 Highly Specialised Drugs Program as Public and Private Hospital Authority Required listings on a cost minimisation basis compared with sildenafil for the treatment of WHO Functional Class III primary pulmonary arterial hypertension and pulmonary arterial hypertension secondary to connective tissue disease. The equi-effective doses are tadalafil 40 mg (2 x 20 mg once daily) and sildenafil 60 mg (20 mg three times a day).

The PBAC agreed that sildenafil is the appropriate comparator as it is the product most likely to be replaced in clinical practice, has the same mechanism of action, and is PBS-listed for the identical patient population as proposed for tadalafil.

The submission presented an indirect comparison between tadalafil (P-HIRST) and sildenafil (SUPER), via placebo, which showed a non-statistically significant difference in the mean change from baseline in 6 minute walk distance (6MWD) 0.03 metres (95% CI: -30.4, 30.3). Indirect comparison analyses for improvement in functional status, clinical worsening and haemodynamic parameters also suggested no statistically significant differences between tadalafil and sildenafil.

The PBAC considered that there are the following uncertainties associated with the indirect comparison such as:

- a small sub-group of the P-HIRST trial population was used in the indirect comparison (reflecting the intended use of tadalafil as monotherapy but not the ITT population) but more than half (53%) of the patient population in the tadalafil trial had concomitant maintenance treatment with bosentan. The SUPER trial did not allow concurrent use of PAH therapies;
- the endpoints of the trials were assessed at different timepoints 16 weeks in the P-HIRST trial and 12 weeks in the SUPER trial;
- the 95% confidence interval of the mean change from baseline in 6MWD is wide; and
- the different mix of WHO functional class II and III patients.

The PBAC considered that although the quality of data is poor, it is probably reasonable to accept that tadalafil is non-inferior to sildenafil in terms of comparative effectiveness and safety. The PBAC also noted that the lower bound of the 95% CI (-30.4 metres) for the indirect comparison is consistent with previously accepted results for listing of oral drugs for PAH. The PBAC noted that tadalafil will be used for a small population and prescribed by specialists and is unlikely to expand the PAH drug market. The PBAC considered that the listing of tadalafil should be cost neutral to the PBS.

The PBAC considered that although the totality of the evidence is weak, it is sufficient to recommend listing.

The PBAC noted the advice of the Highly Specialised Drugs Working Party which supported listing tadalafil as a HSD under Section 100.

Recommendation:
TADALAFIL, tablet, 20 mg

Restriction: **To be finalised**

Maximum qty: 56
Rpt: Nil

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 has no comments.