PUBLIC SUMMARY DOCUMENT

Product: RIOCIGUAT, 500 microgram tablet, 42 and 84, 1 mg tablet, 42 and 84, 1.5 mg tablet, 42 and 84, 2 mg tablet, 42 and 84, and 2.5 mg tablet, 42 and 84, Adempas®
Sponsor: Bayer Australia Ltd
Date of PBAC Consideration: March 2014

1. Purpose of Application

The major submission sought a Section 100 (Highly Specialised Drugs Program) Authority Required listing for the treatment of primary pulmonary hypertension, pulmonary arterial hypertension (PAH) secondary to connective tissue disease and PAH associated with congenital heart disease (CHD) in patients with WHO Functional Class III / 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 PBAC had not previously considered riociguat.

3. Registration Status

The submission was made under the TGA/PBAC parallel process. At the time of PBAC consideration, riociguat had been approved by the Advisory Committee on Prescription Medicines (ACPM) in February 2014. The ratified ACPM outcome was received on 5 March 2014.

Riociguat was TGA registered on the 14 April 2014 for the following indications:

Adempas, as monotherapy or in combination with approved PAH treatments (endothelin receptor antagonists (ERAs) or inhaled or subcutaneous prostanoids), is indicated for the treatment of:

- Idiopathic pulmonary arterial hypertension (IPAH)
- Heritable pulmonary arterial hypertension
- Pulmonary arterial hypertension associated with connective tissue diseases (PAH-CTD)
- Pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) in adult patients with WHO functional Class II, III or IV symptoms
- Chronic thromboembolic pulmonary hypertension

Adempas is indicated for the treatment of:

- Persistent or recurrent chronic thromboembolic pulmonary hypertension (CTEPH) after surgical treatment or inoperable CTEPH in adult patients with WHO functional Class II, lll or IV symptoms

4. Listing Requested and PBAC's View

The submission requested listing on a cost-minimisation basis with bosentan.

The submission requested the same restriction as that for bosentan (with the exception of a "Cessation of Treatment" restriction, which was not requested for riociguat). The PBAC considered this appropriate.

A summarised version of the submission's requested restriction is shown below. It does not meet current electronic media requirements.

Section 100 (Highly Specialised Drugs Program)
Authority Required (Private/Public Hospital) – Written only
Initial
Treatment 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 greater than 8 mmHg, 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 greater than 8 mmHg, as measured by RHC, or, where a RHC cannot be performed on clinical grounds, right ventricular function as assessed by ECHO; OR
(c) WHO Functional Class IV primary pulmonary hypertension; OR
(d) WHO Functional Class IV pulmonary arterial hypertension secondary to connective tissue disease; OR
(e) WHO Functional Class III or IV pulmonary arterial hypertension associated with a congenital systemic-to-pulmonary shunt (including Eisenmenger's physiology).

Maximum Quantity: 42 tablets
Number of Repeats: 0

Authority Required (Private/Public Hospital) – Written only
Continuing treatment
Continuing PBS-subsidised treatment with riociguat of patients who have received approval for initial PBS-subsidised treatment with riociguat and who have been assessed by a physician from a designated hospital to have achieved a response to their most recent course of riociguat treatment.

Maximum Quantity: 84 tablets
Number of Repeats: 5

5. Clinical Place for the Proposed Therapy

PAH is a serious disease that can lead to heart failure and death. It is associated with a marked decrease in exercise tolerance. With the exception of lung transplantation, there is currently no cure for PAH.

The submission proposed riociguat as an alternative treatment option, with a novel mechanism of action, for patients with WHO functional class III or IV severity IPAH, drug induced PAH, familial PAH, PAH-CTD or PAH-CHD.

6. Comparator

The submission nominated bosentan as the main comparator.

The PBAC agreed with the ESC that as riociguat and sildenafil increase cyclic guanosine monophosphate (GMP) and cause smooth muscle relaxation, sildenafil should also considered a comparator.

The PBAC noted the sponsor's pre-PBAC response proposed a mixed comparator of bosentan and sildenafil. The PBAC considered this to be appropriate.

7. Clinical Trials

The submission presented an indirect comparison of riociguat against bosentan, using placebo as the common comparator. The published clinical trials presented in the submission are listed below:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Riociguat vs placebo		
PATENT-1 Ghofrani, H	Riociguat for the treatment of pulmonary arterial hypertension.	*New England Journal of Medicine* 2013; 369 (4): 330-340
Ghofrani, H	Riociguat for the treatment of pulmonary arterial hypertension: A randomized, double-blind, placebo-controlled study (PATENT-1).	*Chest* 2012; 142 (meeting abstract)
Bosentan vs placebo		
BREATHE-1 Rubin LJ	Bosentan therapy for pulmonary arterial hypertension.	*The New England Journal of Medicine* 2002; 346(12):896–03
Study 351 Channick RN	Effects of the dual endothelin receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study.	*Lancet* 2001;358(9288):1119–23 *Revista Portuguesa de Cardiologia* 2001; 20 (11): 1151-1152
Badesch DB	Complete results of the first randomized, placebo-controlled study of bosentan, a dual endothelin receptor antagonist, in pulmonary arterial hypertension.	*Current Therapeutic Research, Clinical & Experimental* 2002; 63(4):227–46
BREATHE-5 Galiè N	Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study.	*Circulation* 2006; 114(1):48–54

The PBAC noted the following concerns about the indirect comparison between the PATENT-1 subgroup and the meta-analysed bosentan trials:

- Exchangeability of the trial populations - the placebo arm in the subgroup of PATENT-1 reported a substantially greater reduction in 6-minute walk distance (6MWD) (-36.7

metres) than that reported in the placebo arms of any of the bosentan trials (-6 to -9.7 metres).

- Consistency of results - the estimate of comparative effectiveness of riociguat versus bosentan for the outcome of 6MWD was not consistent with the results of the indirect comparison on secondary outcomes. More than 60% of placebo patients in the three bosentan trials experienced worsening in WHO function class (FC) compared with only 3.6% in PATENT-1, but this was not consistent with the greater worsening in 6MWD achieved by placebo patients in PATENT-1 compared with the bosentan trials.
- Statistical methodology - the magnitude of the difference in 6MWD between riociguat and placebo may have been influenced by the use of statistical methods to deal with missing data or have been affected by outliers in the placebo arm of PATENT-1.

The sponsor did not request a hearing for this item.

The PBAC noted that no consumer comments were received for this item.

8. Results of Trials

The PBAC noted the following issues with the presented indirect comparison of riociguat with bosentan:

- The change in 6MWD from baseline in the placebo arm of the bosentan trials was substantially different to that in the post hoc defined PATENT-1 subgroup consisting of patients similar to the target PBS population and the population in the bosentan trials.
- Even with use of the PATENT-1 subgroup these trials are not sufficiently interchangeable to support an indirect comparison.
- The comparative treatment effect of riociguat in the indirect comparison - in terms of change from baseline in 6MWD - appeared inconsistent with the direction of effect of some of the secondary efficacy variables.

The change in 6MWD from baseline in the placebo arm of the bosentan trials is substantially different to that in the post-hoc defined PATENT-1 subgroup consisting of patients similar to the target PBS population and the population in the bosentan trials.

The PBAC noted that the submission's methodology to address the issue of missing data was a "worst value imputation" in which the last observed value (not including follow-up) was carried forward for patients who completed the study or withdrew. The worst value (0 m) was imputed in the case of death or clinical worsening without a termination visit or without a measurement at the termination visit.

The sponsor's pre-subcommittee response provided an analysis using only last observation carried forward (LOCF) without imputation of the worst value, however noting that this method potentially underestimates the treatment effect of riociguat due to the fact that baseline 6MWD would be carried forward for patients who withdrew due to clinical worsening or death.

The worst value imputation resulted in a mean difference in 6MWD of 70.8 metres [24.6, 117], while the LOCF analysis resulted in a mean difference of 55.8 metres [27.9, 83.7]. The mean difference for the complete data set was 44.5 metres [18.6, 70.4]. Non-inferiority limits of -35 m and -50 m in 6MWD have previously been accepted by the PBAC. Overall, the

PBAC agreed with the ESC that this additional analysis supported a conclusion of non-inferiority of riociguat to bosentan.

The submission also presented an indirect comparison of riociguat with sildenafil. The PBAC noted that the lower 95% CI for the indirect comparison with sildenafil was -38 metres. When a conservative approach is taken and PATENT-1 complete data is used in the comparison, the lower 95% CI was -40.4.

The PBAC noted the following concerns about the indirect comparison:

- Differences in baseline characteristics of the PATENT-1 treatment naïve WHO FC I-IV subgroup and the ITT population in the SUPER (sildenafil) trial. Patients enrolled in the SUPER trial may have had more severe disease.
- The trial population is broader than is proposed for PBS listing.

The PBAC recalled that in considering sildenafil in November 2006, it accepted that sildenafil and bosentan are non-inferior to one another. The recommendation for sildenafil had been based an indirect meta-analysis of three randomised, double-blind, multi-centre, parallel group trials (one of sildenafil and two of bosentan). The primary outcome was 6MWD.

Overall, the PBAC agreed with the ESC that the data presented in the submission showed that riociguat is likely non-inferior to sildenafil.

The submission did not present an analysis of comparative harms that related directly to the requested PBS target population. The PBAC noted that the indirect comparison of the ITT populations between the trials by way of the common reference (placebo) was difficult to interpret due exchangeability issues between the trials.

The PBAC noted that a significant proportion of patients in the PATENT-1 trial were taking concomitant ERAs, while the population in the bosentan trials were treatment naive. The TGA Clinical Evaluation Report stated that clearance of bosentan was increased by 35.6% in patients taking riociguat. Therefore, the placebo patients in PATENT-1 who were taking a concomitant ERA may have had higher steady-state concentrations of bosentan than those in the riociguat arm so it would be expected that any adverse events associated with bosentan would be higher in the placebo arm (given the relatively lower clearance rate). The comparative safety in the ITT population of PATENT-1 therefore represented a comparison of riociguat with a lower effective dose of bosentan versus placebo with a higher effective dose of bosentan.

The PBAC noted that the inclusion of patients taking concomitant ERAs (i.e. dual therapy) complicated the comparison with the PBS population (in which only a single agent is subsidised). The PBAC therefore considered that the indirect comparison did not reflect the comparative harms of riociguat monotherapy versus bosentan monotherapy.

The PBAC considered that the safety profiles of the drugs, particularly between riociguat and bosentan, are likely to be dissimilar. The PBAC considered however that in practice prescribers will select PAH treatments to suit a patient's tolerance and patients are closely supervised.

9. Clinical Claim

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

The PBAC considered that the claim of non-inferior comparative effectiveness was adequately supported, notwithstanding the identified issues with the indirect comparison. The PBAC also considered that riociguat is non-inferior to sildenafil.

The PBAC considered that the claim of non-inferior comparative safety was difficult to assess in light of exchangeability issues between the trials in the indirect comparison. The PBAC concluded overall that this claim was reasonable, however that the safety profiles of the individual drugs were likely to be different.

10. Economic Analysis

The submission presented a cost-minimisation analysis of riociguat with bosentan. The following equi-effective doses were derived from the indirect comparison:

- Individual titration of riociguat (1 mg tid to 2.5 mg tid) and bosentan 62.5 mg bid or 125 mg bid
- Individual titration of riociguat (1 mg tid to 2.5 mg tid) and sildenafil 20 mg tid.

The submission claimed cost-offsets to the MBS due to a reduction in liver function testing (LFT) associated with the use of bosentan. The data provided in the submission did not support a claim of superior safety, which the PBAC considered was implicit when claiming a reduction in required safety monitoring. The PBAC noted that liver function tests may be routinely requested for patients with PAH who are taking riociguat due to concurrent illness, concomitant therapy or because they are also taking bosentan, and considered that in these circumstances, no cost-savings associated with a reduction in LFTs would be realised.

The DPMQ was estimated in the submission to satisfy a cost-neutral substitution with bosentan, accounting for the cost of liver function tests for each month (30 days) of treatment with bosentan. The method used in the submission was complicated and departed from the approach recommended in the PBAC Guidelines; however the calculated DPMQ was very close to that recalculated using the simplified approach recommended in the PBAC Guidelines.

The submission's base case cost-minimisation analysis assumed that 100% of patients prescribed riociguat would otherwise have taken bosentan. The submission also presented an analysis in which riociguat substitutes for other PAH agents dependent upon their market share.

The PBAC agreed with the submission that the listing of riociguat should be cost-neutral to the PBS, and considered it appropriate to take a conservative approach with riociguat utilisation replacing bosentan and replacing sildenafil.

11. Estimated PBS Usage and Financial Implications

The submission estimated less than 10,000 patients accessing riociguat in year 5. The submission estimated a net cost to the PBS of less than $10 million but that this cost would be completely offset by a reduction in LFTs performed when riociguat replaces bosentan.

The submission assumed that the PBS listing of riociguat would be cost neutral to the Commonwealth.

In estimating the MBS costs, the submission did not take into account the cost associated with specialist visits for dose adjustment, and incorrectly included patient co-payments. The PBAC considered that this overestimated the proposed cost savings to the MBS.

The PBAC noted that the costs to the PBS/RPBS could be greater if the uptake of riociguat is higher than the submission's estimate.

The PBAC noted that the substitution pattern of riociguat for other agents has a significant influence on the financial impacts to the PBS. The PBAC noted that at the requested price, the costs to the PBS/RPBS could be greater if riociguat substitutes for other agents. The PBAC did not accept the assumption that riociguat will only replace bosentan.

12. PBAC Outcome

The PBAC recommended the listing of riociguat, on the basis that is should be available only under special arrangements under Section 100 (Highly Specialised Drugs Program).

The PBAC recommended listing on a cost-minimisation basis, with the equi-effective doses being individual titration of riociguat (1 mg tid to 2.5 mg tid) and bosentan 62.5 mg bid or 125 mg bid, and individual titration of riociguat (1 mg tid to 2.5 mg tid) and sildenafil 20 mg tid.

The PBAC considered that a mixed comparator was appropriate. The submission claimed that riociguat is non-inferior to bosentan in both comparative effectiveness and comparative safety. The PBAC considered that these claims were reasonable, noting however the issues relating to the indirect comparison. The PBAC also considered that riociguat is non-inferior to sildenafil.

The PBAC recommended that the Safety Net 20 Day Rule should not apply to riociguat.

The PBAC advised that, under Section 101 (3BA) of the *National Health Act*, riociguat should not be treated as interchangeable with any other drug on an individual patient basis.

Recommendation:
Add new items:

Restriction 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

Bayer welcomes the positive recommendation from the PBAC for Adempas and hopes to continue working collaboratively with the Department of Health to bring access to Australian patients as soon as possible.