

5.10 RIOCIQUAT

**Tablets; 0.5 mg, 1 mg, 1.5 mg and 2 mg;
Adempas®; Bayer Australia Ltd.**

1 Purpose of Application

- 1.1 The submission seeks an Authority Required listing for riociguat for the treatment of inoperable or persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) after a pulmonary endarterectomy.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Manufacturer	Name and
RIOCIQUAT 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg tablets, 42	1	0	Adempas®	Bayer
RIOCIQUAT 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg, 2.5 mg, tablets, 84	1	5		

Authority required

For the treatment of inoperable or persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) post-pulmonary endarterectomy (PEA) in the patients with WHO Functional Class II-IV and a mean right atrial pressure (RAP) of ≤ 8 mmHg.

- 2.1 The evidence base for the requested listing is a randomised controlled trial (CHEST-1) comparing riociguat with placebo in patients with CTEPH. The submission did not provide any economic evaluation of riociguat compared with placebo.
- 2.2 It may be appropriate for the requested restriction for CTEPH to be listed under Section 100 (Highly Specialised Drug Program) to be consistent with the recommended restriction of riociguat for PAH. The submission has acknowledged the sponsor's willingness to work with the Restrictions Working Group to refine the proposed wording of the restriction.
- 2.3 The sponsor confirmed in the Pre-Sub-Committee response that the proposed eligibility criterion of a right atrial pressure (RAP) of ≤ 8 mmHg in the requested listing was a typographical error.

3 Background

- 3.1 Riociguat was TGA registered in April 2014 for both PAH and CTEPH. The requested PBS restriction is broadly consistent with the TGA approved indication for CTEPH.

- 3.2 This is the first PBAC submission of riociguat for the treatment of inoperable CTEPH or persistent chronic CTEPH after pulmonary endarterectomy.
- 3.3 At the March 2014 meeting, the PBAC recommended listing riociguat for the treatment of Pulmonary Hypertension Group 1, called Pulmonary Arterial Hypertension (PAH): primary or Idiopathic PAH, PAH secondary to connective tissue disease and PAH associated with congenital heart disease (CHD) in patients with WHO Functional Class III/IV. The PBAC accepted that riociguat was non-inferior to both bosentan and sildenafil. The PBAC recommended that riociguat be listed on a cost-minimisation basis, with the equi-effective doses being individual titration of riociguat (1 mg tid to 2.5 mg tid) relative to bosentan 62.5 mg bid or 125 mg bid, or individual titration of riociguat (1 mg tid to 2.5 mg tid) relative to sildenafil 20 mg tid. The PBAC considered that riociguat should be available only under special arrangements under Section 100 (Highly Specialised Drugs Program).

4 Clinical place for the proposed therapy

- 4.1 CTEPH (PH Group 4) is a progressive disease where pulmonary vascular resistance increases progressively ultimately resulting in right heart failure and death.
- 4.2 Pulmonary endarterectomy is a potentially curative surgical intervention for CTEPH. Riociguat is indicated for CTEPH patients who cannot receive pulmonary endarterectomy (inoperable) or those who have persistent CTEPH after surgery. The proposed listing also requests that patients must have failed to respond to 6 or more weeks of appropriate vasodilator treatment unless they are intolerant or a contraindication to such treatment exists.

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

- 5.1 The submission nominates placebo as the main comparator. The ESC considered this is appropriate, but noted, in clinical practice, that other PAH treatments may be used off-label.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the issue of misdiagnosing CTEPH with PAH, leading to CTEPH patients potentially denied curative procedures. The clinician also highlighted the natural history of the disease, how the drug would be used in practice, and addressed other matters in response to the Committee's questions.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (3) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described the need for ease of accessibility as well as concerns about price of treatment. The PBAC specifically noted the letter sent on behalf of the members of Pulmonary Hypertension Association Australia advising that the inclusion of riociguat for CTEPH would enable greater access for patients, reducing overall impact on individuals, families and the community.

Clinical trials

- 6.3 The submission is based on one head-to-head randomised trial (CHEST-1) comparing riociguat to placebo (n=261) and one supplementary long term extension study (CHEST-2) (n=182) to CHEST-1. Both arms have background treatment of best supportive care. CHEST-2 was a single arm study that assesses the long-term safety/tolerability of riociguat and provides limited evidence of comparative efficacy versus placebo.
- 6.4 Details of the CHEST-1 trial are provided in the following table.

Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
CHEST-1	Clinical Study Report Randomised, double-blind, placebo-controlled, multicentre, multi-national study to evaluate the efficacy and safety of oral BAY 63-2521 (1 mg, 1.5 mg, 2 mg or 2.5 mg tid) in patients with chronic thromboembolic pulmonary hypertension (CTEPH).	30 th Oct 2012
	Publications Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, Mayer E, Simonneau G, Wilkins MR, Fritsch A, Neuser D, Weimann G and Wang C. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. Jansa P, Ghofrani H-A, Hoeper MM, Kim NH, Mayer E, Neurohr C, et al. Comparison of hemodynamic parameters in patients with inoperable and persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) in the Phase III CHEST-1 study.	New England Journal of Medicine 2013; 369(4):319-29 European Heart Journal 2013; 34 (suppl 1): 187
	Conference Abstract Ghofrani HA, Hoeper MM, Halank M, Meyer FJ, Stahler G, Behr J, Ewert R, Weinmann G, Neuser D, and Grimminger F. Riociguat For Chronic Thromboembolic Pulmonary Hypertension And Pulmonary Arterial Hypertension: Long-Term Safety, Tolerability, And Efficacy [Abstract] Mayer E, D'Armini AM, Ghofrani H-A, Grünig E, Jansa P, Kim NH, Simonneau G, Torbicki A, Wang C, Wilkins MR, Davie N, Fritsch A and Hoeper MM. Riociguat for the treatment of inoperable CTEPH or persistent/recurrent PH after pulmonary endarterectomy (PEA): A responder analysis from the phase III CHEST-1 study [Abstract] Ghofrani HA, Grimminger F, Hoeper MM, Nick K, Meyer E, Neuser D,	American Journal of Respiratory and Critical Care Medicine 2012; 185: A2370 European Respiratory Society Annual Congress 2013; Sept.7.11, Barcelona, Spain 2013 Chest 2012; 142

	Pena J, Simonneau G and Wilkins M. Riociguat for the treatment of inoperable chronic thromboembolic pulmonary hypertension: A randomized, double-blind, placebo-controlled study (CHEST-1)	(4_MeetingAbstracts):1023A
CHEST-2	<p>Clinical Study Report Long-term extension, multi-centre, multi-national study to evaluate the safety and tolerability of oral BAY 63 2521 (1 mg, 1.5 mg, 2 mg or 2.5 mg tid) in patients with Chronic Thromboembolic Pulmonary Hypertension (CTEPH).</p> <p>Conference Abstract Simonneau G, D'Armini AM, Ghofrani HA, Grimminger F, Hoeper MM, Jansa P, Nick K, Wang C, Wilkins M, Fritsch A, Davie N, Weimann G and Meyer E. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH): 1-year results from the CHEST-2 long-term extension study.</p> <p>Wang c, D'Armini A, Ghofrani HA, Grimminger F, Hoeper M, Jansa P, Kim N, Simonneau G, Torbicki, Wilkins M, Fritsch A, Davie N and Mayer E. Long-term riociguat treatment in inoperable and persistent/recurrent CTEPH patients in who functional class (FC) I/II versus FC III/IV at baseline: Results from the 16-week phase III CHEST-1 study and CHEST-2 open-label extension.</p>	<p>3rd May 2012</p> <p>Chest 2014; 145 (3) (4_MeetingAbstracts):1023A</p> <p>Chest 2014; 145 (3Suppl):535B</p>

Source: Table B.2-2, p28 of the submission

6.5 The key features of the direct randomised trial are summarised in the following table.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome
Riociguat vs. placebo					
CHEST-1	261	R, DB 16 weeks	Low*	CTEPH	6MWD

R=randomised; DB=double blind; 6MWD = 6-minute walk distance; CTEPH = chronic thromboembolic pulmonary hypertension. *Based on the information provided in the submission (unequal distribution of baseline characteristics is found, but difficult to assess its impact on the treatment effect). Source: compiled during the evaluation

Comparative effectiveness

6.6 The following table presents the changes in 6MWD reported in CHEST-1. For the intention-to-treat (ITT) analysis, there was a statistically significant treatment effect in terms of change in 6MWD from baseline, favouring riociguat over placebo. The mean difference in change of 6MWD between the treatment groups was 45.7 metres. This is a small-to-moderate difference, favouring riociguat, when considered in the context of the average distance walked at baseline in both groups (approximately 350 metres) and the duration of CHEST-1 (16 weeks). Most haemodynamic measures (mean pulmonary artery pressure, systolic pulmonary artery pressure, diastolic pulmonary artery pressure, mean systemic arterial blood pressure, mixed venous oxygen-saturation, cardiac output, cardiac index, pulmonary vascular resistance, pulmonary vascular resistance index, systemic vascular resistance and systemic vascular resistance index) were statistically significantly improved in patients receiving riociguat compared to placebo.

Results of mean change in 6MWD (metres) from baseline for CHEST-1

Trial ID	Riociguat N=173 mean ± SD		Placebo N=88 mean ± SD		Least Square Mean difference in change of 6MWD (95% CI)	p-value
	Baseline 6MWD	Change from baseline	Baseline 6MWD	Change from baseline		
CHEST-1	342.3±81.9	38.9±79.3	356±74.7	-5.5±84.3	45.69 (24.74, 66.63)	<0.0001

6MWD = 6-minute walk distance; SD = standard deviation; CI = confidence interval.

Outcomes measured over 16 weeks

Source: Table B.6-1, p87 of the submission

- 6.7 The following table summarises the CHEST-1 results for change in WHO Functional Class from baseline to Week 16. Improvement of at least one WHO Functional Class is shown in 33% of riociguat-treated patients compared with 15% receiving placebo. The riociguat arm was twice as likely as the placebo arm to improve 1 or 2 functional classes (RR 2.2, 95%CI 1.28, 3.80). This is likely to be a clinically meaningful difference. However, the proportion of patients who were either stable or showed improvements in WHO Functional Class was similar between the riociguat arm (164/173=94.8%) and the placebo arm (81/87=93.1%). The proportion of patients who deteriorated, that is an increase of at least one class, was also similar between the randomised treatment groups (5.2% in riociguat vs 6.9% in placebo).

Change (number of classes) in WHO Functional Class from baseline to Week 16 in ITT analysis set

Change in number of classes	Riociguat 1.0- 2.5mg n=173	Placebo n=87
-2	4 (2.3)	0 (0)
-1	53 (30.6)	13 (14.9)
0	107 (61.8)	68 (78.2)
1	7 (4.0)	3 (3.4)
2	1 (0.6)	3 (3.4)
3	1 (0.6)	0 (0)
Improvement of ≥ 1 class* (95%CI): Riociguat (32.9%) versus placebo (14.9%)	Relative risk 2.2 (1.28, 3.80) Risk difference 18% (7.7%, 28.3%) p-value (stratified Wilcoxon test) = 0.0026	

Relative risk and risk difference were calculated during the evaluation using Stata 12.

*Improvement by -1 and -2 summed in each treatment group; ITT = intention to treat; CI = confidence interval

Source: Table B.6-6, p95 of the submission

Comparative harms

- 6.8 Adverse events (AEs) reported in the CHEST-1 trial are summarised below. Treatment related emergent adverse events (TEAEs) were higher in the riociguat group compared to the placebo group. The most commonly experienced events associated with riociguat were headache, dizziness, dyspepsia and hypotension. Overall, riociguat is associated with an increased risk of AEs compared with placebo. Data (including those from the CHEST-2 extension study) provided in the submission do not suggest any additional safety concerns associated with riociguat.

Summary of key adverse events in the CHEST-1 trial

	Riociguat (N=173) n (%)	Placebo (N=88) n (%)	RR (95% CI)	RD% (95% CI)
AE (any)	160 (92.5)	78 (88.6)	1.04 (0.96, 1.14)	3.8 (-3.9, 11.6)
TEAE (any)	159 (91.9)	76 (86.4)	1.06 (0.97, 1.17)	5.5 (-2.3, 13.8)
Discontinuation because of AE	5 (2.9)	2 (2.3)	1.27 (0.25, 6.42)	0.62 (-3.4, 4.6)
Any TEAE leading to death	2 (1.2)	3 (3.4)	0.34 (0.06, 1.99)	-2.3 (-6.4, 1.9)
Serious TEAE (any)	34 (19.7)	14 (15.9)	1.24 (0.70, 2.18)	3.7 (-5.9, 13.4)
Drug-related TEAEs (≥5% of subjects in either treatment arm)				
- Headache	27 (15.6)	7 (8.0)	1.96 (0.89, 4.33)	7.7 (-0.17, 15.4)
- Dizziness	26 (15.0)	3 (3.4)	4.41 (1.37, 14.16)	11.6 (5.1, 18.2)
- Dyspepsia	21 (12.0)	6 (7.0)	1.78 (0.75, 4.25)	5.3 (-1.8, 12.5)
- Nausea	11 (6.4)	5 (5.7)	1.12 (0.40, 3.12)	0.68 (-5.4, 6.7)
- Hypotension	14 (8.1)	0 (0.0)	NC	8.1 (2.3, 13.9)
- Peripheral oedema	5 (2.9)	8 (9.1)	0.32 (0.11, 0.94)	-6.2 (-12.7, 0.3)

Relative risk and risk difference were calculated during the evaluation using Stata 12. **Values in bold represent statistically significant differences observed between groups.** RR = relative risk; RD = relative difference; AE = adverse event; TEAE = treatment emergent adverse event; NC = not calculable Source: Table B.6-11, p105 and Table B.6-12, p106 of the submission

Benefits/harms

- 6.9 A summary of the comparative benefits and harms for riociguat versus placebos presented in the following table.

CHEST-1: Summary of comparative benefits and harms of riociguat relative to placebo over 16 weeks

Benefits							
Change in 6MWD (metres)							
Riociguat			Placebo			LS Mean difference: Riociguat vs. placebo (95% CI)	
n	Mean Δ baseline	SD*	N	Mean Δ baseline	SD*		
173	38.9	79.3	88	-5.5	84.3	45.69 (24.74, 66.63)	
Change by ≥1 WHO Functional class							
Riociguat		Placebo		RR (95% CI)	Event rate/100 patients		RD (95% CI)
					Riociguat	Placebo	
57/173		13/88		2.2 (1.28, 3.80)	33	15	18 (7.7, 28.3)
Harms							
	Riociguat	Placebo	RR (95% CI)	Event rate/100 patients		RD (95% CI)	
				Riociguat	Placebo		
Dizziness	26/173	3/88	4.41 (1.37, 14.16)	15	3.4	11.6 (5.1, 18.2)	
hypotension	14/173	0/88	NC	8.1	0	8.1 (2.3, 13.9)	
Headache	27/173	7/88	1.96 (0.89, 4.33)	16	8	7.7 (-0.17, 15.4)	

LS = least square; NC= not calculable; 6MWD = 6-minute walk distance; SD = standard deviation; RD = risk difference; RR = risk ratio; CI = confidence interval. Source: Compiled during the evaluation

- 6.10 On the basis of direct evidence presented by the submission, treatment with riociguat, in comparison to placebo, over 16 weeks results in:
- An average increase of 46 metres in the distance able to be walked in 6 minutes. Both treatment groups were able to walk approximately 350 metres in 6 minutes at the beginning of the study. The PBAC has previously accepted a minimum

- clinically important difference in 6MWD of between 35-50m.
- An estimated 18 additional patients with an improvement by ≥ 1 WHO Functional class for every 100 patients.
 - An estimated 12 additional patients with dizziness for every 100 patients.
 - An estimated 8 additional patients with hypotension for every 100 patients.
 - An estimated 8 additional patients with headache for every 100 patients.

Clinical claim

- 6.11 The submission describes the effectiveness and safety of riociguat in the following manner: “The comparative effectiveness and safety for riociguat in the PBAC recommended PAH population is equivalent to the effectiveness and safety for riociguat in the proposed CTEPH population”, based on the following evidence:
- Indirectly comparing the clinical outcomes (change in 6MWD and change in PVR from baseline) in the CHEST-1 trial with that in the PATENT-1 trial (riociguat in patients with PAH compared with placebo), and
 - comparing the burden of illness (in terms of quality of life (QoL) at baseline and mortality) between patients with CTEPH and PAH based on a literature review.
- 6.12 The submission claims that the comparative primary efficacy results of both PATENT-1 and CHEST-1 trials indicate equivalent effectiveness of riociguat in both PAH and CTEPH study population. The ESC considered that the claim of equivalent effectiveness may not be supported. The improvements in 6MWD cannot be compared across studies with differing population, prognostic and disease characteristics. The same functional improvement in 6MWD from baseline in the PAH and CTEPH populations could have different clinical implications in terms of functional class changes and overall survival because the diseases and population characteristics are different, particularly given that change in 6MWD is a surrogate outcome and baseline 6MWD is a prognostic factor.
- 6.13 Using the framework for evaluating proposed surrogate measures, as presented in the Report of the Surrogate to Final Outcome Working Group to the Pharmaceutical Benefits Advisory Committee, the ESC considered that the submission had not demonstrated 6MWD as a valid surrogate for the target clinical outcomes in CTEPH ie improved exercise capacity/function and overall survival.
- 6.14 The submission also claims that baseline QoL and mortality are similar across patients with CTEPH and PAH, in spite of the differences in study design and patient populations in the studies included in the literature review. No statistical comparisons are presented to support this claim. The evidence relating to QoL and mortality in both CTEPH and PAH populations varied widely across the studies but the submission argues it is due to the range of study types included in the review. The claimed comparability of QoL and mortality in both populations remains uncertain due to the differences in the study design, patient population and disease characteristics.
- 6.15 Based on the evidence presented from the CHEST-1 trial, riociguat is superior to placebo in terms of comparative effectiveness measured using the primary outcome of change in 6MWD from baseline, and inferior to placebo in terms of comparative safety.

- 6.16 The ESC noted in the Submission and in the Pre-Sub-Committee Response (PSCR, p1) that the rationale of the submission and the clinical claim follows the precedent of the March 2008 recommendation of bosentan for Eisenmenger's Syndrome. However, the ESC noted that the precedent in bosentan referred to the same subcategory of pulmonary hypertension (Group 1: PAH), whereas the current submission for riociguat seeks an extension from one subcategory (Group 1: PAH) to another (Group 4: CTEPH). The ESC noted that the pathophysiology of PAH and CTEPH differ: PAH is a disorder of the small muscular arterioles of the pulmonary circulation by inflammatory and unknown mechanisms; CTEPH is due to chronic occlusion of proximal and distal arteries by blood clots.

Economic analysis

- 6.17 The submission does not provide any economic analysis of riociguat compared with placebo in patients with CTEPH. Instead, the submission assumes that the cost effectiveness of riociguat in patients with CTEPH is similar to that previously demonstrated in patients with PAH. In the absence of the type of economic evaluation that is consistent with the 2013 PBAC Guidelines, the value for money of riociguat treatment of patients with CTEPH, relative to placebo, is unknown.

- 6.18 [REDACTED] The ESC further considered that an economic evaluation of riociguat compared to placebo, using the proposed effective price, should have been presented to determine the cost effectiveness of riociguat in this population.

Drug cost/patient/year: [REDACTED]

- 6.19 The submission assumes that on average there will be 10 scripts per patient per year. The proposed confidential effective DPMQ (public hospital) is [REDACTED] for all strengths. Therefore the total cost of riociguat per patient per year is estimated to be [REDACTED]. Assuming maximum compliance, a total of 13 scripts would be required per patient and the total cost per patient per year would be [REDACTED].

Estimated PBS usage & financial implications

- 6.20 The item was considered by DUSC.

- 6.21 The submission takes an epidemiological approach to estimate the market size. The estimated use of riociguat and the financial implications are summarised below. The submission estimates that the cost of riociguat (using effective DPMQ) to the PBS will be less than \$10 million per year in Year 1, increasing to \$10-20 million per year in Year 5 of listing.

Estimated use and financial implications

Year	2015	2016	2017	2018	2019
Patients likely to be treated	■	■	■	■	■
Total number of prescriptions (all strengths)*	■	■	■	■	■
Net cost to the PBS**	■	■	■	■	■

*Average number of scripts /patient/year estimated in the submission = 10

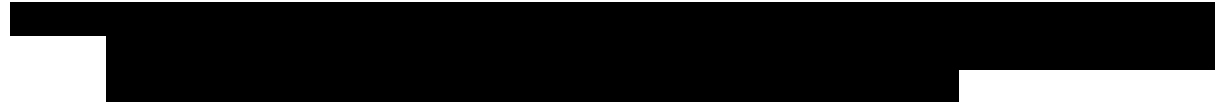
**Costs were calculated using the effective Public Hospital DPMQ per pack of 84 tablets ■

No costs to the MBS are estimated in the submission.

Source: Table E.2-5 and Table E.2-6, p154 of the submission

- 6.22 The DUSC considered that a reasonable approach was taken to derive the estimates presented in the submission. The DUSC considered the main issues were:
- Overall CTEPH prevalence in years 2 to 5 is likely to be significantly overestimated, as it relies on a prevalence estimate from a study by Strange et al; which, according to the submission, is likely to significantly overestimate CTEPH prevalence. DUSC expressed some concern that the Strange et al study relied on a retrospective analysis of an echocardiography database, given that echocardiography is a less accurate method for CTEPH diagnosis than right heart catheterisation.
 - Diagnosis rate: while CTEPH could potentially be underdiagnosed, no source is provided to justify the rapidly increasing diagnosis rate in years 2 to 5. DUSC considered the diagnosis rate in year 1 to be a reasonable estimate (based on a survey of 12 physicians) and the rates in years 2 to 5 an overestimate.
 - Uptake (30% in year 1 to 90% in year 5 of the listing) is likely to be underestimated in the first two years of listing, as there is an existing pool of patients with persistent or inoperable CTEPH appropriate for medical treatment, and this group of patients are likely to be trialled on this drug quickly.
- 6.23 DUSC considered the year 1 utilisation may be an underestimate; and the estimates for year 2 to year 5 an overestimate. Use may be beyond expectations in year 1 due to an underestimated uptake rate. Over the five year estimates use is not likely to be beyond the estimates.
- 6.24 In the pre-PBAC response, patient numbers and financial estimates were updated in line with the DUSC Advice. The cost of riociguat to the PBS estimated to be less than \$10 million per year in Year 1, increasing to less than \$10 million per year in Year 5 of listing.

Financial Management – Risk Sharing Arrangements

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- 6.25 The ESC noted the Sponsor's willingness to enter into a risk-share arrangement with the Commonwealth to provide further certainty regarding the financial impact of listing riociguat for the treatment of CTEPH.

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

- 7.1 The PBAC rejected the Authority Required listing for riociguat for the treatment of inoperable or persistent/recurrent chronic thromboembolic pulmonary hypertension after a pulmonary endarterectomy, as the cost-effectiveness of riociguat for this indication had not been established against the appropriate comparator.
- 7.2 The PBAC agreed that placebo is the appropriate comparator in this place of therapy, although noting that, in clinical practice, other PAH treatments such as bosentan and sildenafil may be used off-label. The PBAC noted that the pre-PBAC response highlighted that international clinical guidelines (European Society of Cardiology and the European Respiratory Society 2009 guidelines) recommend the use of PAH-specific therapies (predominantly endothelin receptor antagonists) for those patients deemed inoperable or have recurrent/persistent CTEPH.
- 7.3 The PBAC noted the statistical significance of the treatment effect in terms of the primary endpoint of change in 6MWD favouring riociguat over placebo. The PBAC recalled that it has previously considered the 6MWD as an endpoint in a number of submissions of pulmonary arterial hypertension (PAH) treatments. The committee further noted that the mean difference (45.7 metres) is within the Minimal Clinically Important Difference (MCID) of 35 – 50 metres it had previously accepted. The submission uses the change in the 6MWD from baseline as a surrogate outcome to measure the exercise capacity and functionality in patients with CTEPH disease. In addition, the submission states that there is a strong relationship between the improvement in the 6MWD and survival gain. The PBAC noted that the submission presented a post-hoc analysis to explore the predictive nature of the 6MWD for overall survival within the CHEST trials, the results indicated that for each additional change of 40m provided by riociguat, therapy, the risk of dying is decreased by 36.2% (95%CI 12.6, 53.5). The pre-PBAC response stated that the risk of dying is decreased by 47.0% (95%CI 24.9, 62.6) for every 40m gain from baseline while on riociguat therapy when age, gender, height, weight are included in the analysis. The PBAC considered that changes in the 6MWD are likely to predict a survival gain, but was not confident in the magnitude of the effect due to the post-hoc nature of the analysis. The Committee also noted that the latest analyses provided by the sponsor had not been verified. The PBAC noted that there is a lack of consensus on whether the 6MWD is an acceptable or valid surrogate for overall survival (Ventetuolo et al, Proceedings of the American Thoracic Society, 2008 Jul 15;5(5):617-22).

- 7.4 The PBAC recalled in March 2014 that listing of riociguat was recommended 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. The PBAC did not accept the claim that the comparative effectiveness and safety for riociguat in the previously recommended PAH population is equivalent to the effectiveness and safety for riociguat in the proposed CTEPH population. The PBAC considered that the same functional improvement in 6MWD from baseline in the PAH and CTEPH populations cannot be assumed to have the same clinical implications in terms of functional class changes and overall survival because the diseases and trial population characteristics are different. Patients with inoperable or persistent/recurrent CTEPH after a pulmonary endarterectomy are likely to be a more severe group and it is unlikely that the relative risk reduction remains constant across both populations.
- 7.5 The PBAC reiterated that an economic evaluation against the appropriate comparator was the most appropriate option for determining cost-effectiveness of a medicine for listing on the PBS. At this time, the value for money of riociguat treatment of patients with CTEPH, relative to placebo, is unknown.
- 7.6 The PBAC noted that the cost-effectiveness of riociguat for the treatment of inoperable or persistent/recurrent CTEPH after a pulmonary endarterectomy should be established in a major submission.
- 7.7 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 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.

9 Sponsor's Comment

Bayer is disappointed with the rejection, however is strongly committed to working with the PBAC and the Department of Health, in order to bring access to Australian patients who are suffering from this life threatening disease.