7.08 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, 2.5 mg tablet, 42 and 84, Adempas®, Bayer Australia Ltd

1 Purpose of Application

1.1 The re-submission requested Section 100, Authority required listing for riociguat for the treatment of inoperable chronic thromboembolic pulmonary hypertension (CTEPH) or persistent CTEPH subsequent to pulmonary endarterectomy (PEA).

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to an abbreviated version of the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
RIOCIGUAT				Adempas® BN
0.5 mg tablet	42	0		
1.0 mg tablet			$[redacted] (Public hospital)	
1.5 mg tablet			$[redacted] (Private hospital)	
2.0 mg tablet			$[redacted] (Effective price)	
2.5 mg tablet				

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	*Chronic*
Severity:	~~WHO Functional Class II-IV~~
Condition:	~~Inoperable~~ *thromboembolic pulmonary hypertension* ~~CTEPH or Persistent CTEPH subsequent to PEA~~
PBS Indication:	*Chronic thromboembolic pulmonary hypertension*
Treatment phase:	Initial treatment
Restriction Level / Method:	☒Authority Required - In Writing
Treatment criteria:	~~Persistent or recurrent CTEPH after surgical treatment or inoperable CTEPH in adult patients with WHO functional Class II, III or IV symptoms~~

Clinical criteria:	*Patient must have WHO functional class II, III or IV symptoms,* *AND* Patient must have been assessed by a physician *at* ~~from~~ a designated hospital, AND Patient must have diagnosis of inoperable *chronic thromboembolic pulmonary hypertension* (CTEPH) assessed by local expert *pulmonary endarterectomy (*PEA*)* centre, ~~with~~ ~~– RHC demonstrating PVR of >300 dyn*sec*cm^{-5} measured at least 90 days after start of full anticoagulation, AND~~ ~~– PAPmean >25 mmHg, OR~~ ~~– Right ventricular function assessed by echocardiography (ECHO) demonstrating right ventricular dysfunction where a RHC cannot be performed on justifiable clinical grounds,~~ OR Patient must have diagnosis of persistent *chronic thromboembolic pulmonary hypertension* (CTEPH) subsequent to *pulmonary endarterectomy (*PEA*)*. ~~with~~ ~~– RHC demonstrating a PVR >300 dyn*sec*cm^{-5} measured at least 180 days after surgery, OR~~ – ~~Right ventricular function assessed by echocardiography (ECHO) demonstrating right ventricular dysfunction where a RHC cannot be performed on justifiable clinical grounds.~~
Population criteria:	*Patient must be an adult.*

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
RIOCIGUAT 0.5 mg tablet 1.0 mg tablet 1.5 mg tablet 2.0 mg tablet 2.5 mg tablet	84	5	$[redacted] (Public hospital) $[redacted] (Private hospital) $[redacted] (Effective price)	Adempas® BN

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	*Chronic*
Severity:	~~WHO Functional Class II-IV~~
Condition:	~~Inoperable~~ *thromboembolic pulmonary hypertension* ~~CTEPH or Persistent CTEPH subsequent to PEA~~
PBS Indication:	*Chronic thromboembolic pulmonary hypertension*
Treatment phase:	Continuing treatment
Restriction Level / Method:	Authority Required - In Writing
Treatment criteria:	~~Persistent or recurrent CTEPH after surgical treatment or inoperable CTEPH in adult patients with WHO functional Class II, III or IV symptoms~~

Clinical criteria:	Patients must have *previously* received approval for initial PBS-subsidised treatment with this drug AND Patient must have been assessed by a physician from a designated hospital to have achieved a response to their most recent course of treatment with this agent AND Patient must undergo assessment of the following tests every 6 months: (i) RHC composite assessment; and/or (ii) ECHO composite assessment; and (iii) 6MWT

2.2 The re-submission sought listing for riociguat on the basis of a cost utility analysis comparing riociguat to placebo for patients with inoperable CTEPH and patients with persistent CTEPH following PEA, with these patient cohorts modelled separately. This was different to the July 2015 re-submission, which modelled a combined patient cohort.

2.3 The submission requested a Special Pricing Arrangement with an effective price of $[redacted] for initial treatment and $[redacted] for continuing treatment. The pre-PBAC response for the July 2015 re-submission offered the same effective price of $[redacted] for continuing treatment, representing a [redacted]% price reduction from the continuing treatment price requested in the July 2015 re-submission. The pre-PBAC response (p3) for the current re-submission offered an additional [redacted]% price reduction for the continuing treatment (84 tablets) pack of riociguat resulting in an effective AEMP of $[redacted].

2.4 Compared with the July 2015 re-submission, the requested restriction no longer included a requirement for prior vasodilator treatment. This amendment was appropriate, given that prior vasodilator treatment appears to inappropriately require the use of inferior or unsubstantiated treatments prior to riociguat (July 2015 PSD, paragraph 2.3).

2.5 The proposed initial and continuing response measurements for right heart catheterisation (RHC), pulmonary arterial pressure (PAPmean) and echocardiogram (ECHO) were inclusion criteria in the CHEST-1 trial. These were appropriate to include as part of the assessment of eligibility for treatment of patients with CTEPH or persistent CTEPH.

2.6 The re-submission did not include the 6-minute walking distance (6MWD) test as a diagnostic criteria of eligibility. The re-submission stated that while 6MWD should be measured at baseline, that RHC and haemodynamic evaluation are most important for the confirmatory diagnosis of eligibility.

2.7 The re-submission proposed that the requirement for assessment of operability is confirmed by a local expert PEA centre. This served, in part, to address a concern raised during the evaluation of the July 2015 re-submission (July 2015 PSD, paragraph 2.3) regarding the determination of inoperable CTEPH.

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

3 Background

3.1 The TGA registered riociguat for the treatment of patients with pulmonary arterial hypertension (PAH) and CTEPH in April 2014.

3.2 Riociguat received a positive PBAC recommendation for the treatment of PAH in March 2014, however, it was not listed on the PBS for PAH at the time of PBAC consideration of this re-submission (March 2016).

3.3 Riociguat for the treatment of inoperable CTEPH or persistent CTEPH following PEA was previously considered by the PBAC in November 2014 and again in July 2015.

- At the November 2014 meeting, the PBAC rejected the submission on the basis that the cost-effectiveness of riociguat for CTEPH had not been established against the appropriate comparator. The PBAC did not accept the claim that the comparative effectiveness and safety for riociguat in the previously recommended PAH population was equivalent to the effectiveness and safety for riociguat in the proposed CTEPH population. The PBAC considered that the same functional improvement in the 6MWD from baseline in the PAH and CTEPH populations could not be assumed to have the same clinical implications in terms of functional class changes and overall survival because of differences in the diseases and trial population characteristics (November 2014 PSD, paragraph 7.4).
- At the July 2015 meeting, the PBAC rejected the request to list riociguat on the PBS under Section 100 (Highly Specialised Drugs Programme) for the treatment of patients with inoperable CTEPH or persistent CTEPH following PEA on the basis of uncertain cost effectiveness compared with placebo (July 2015 PSD, paragraph 7.1). The following table presents a comparison of the November 2014 and July 2015 submissions with the current re-submission.

Table 1: Summary of key components of the November 2014 submission, the July 2015 re-submission and the March 2016 re-submission

	November 2014 submission	July 2015 re-submission	March 2016 re-submission
Requested restriction	Treatment of inoperable or persistent/recurrent CTEPH post PEA in patients with WHO functional class II-IV and a mean RAP of ≤8mmHg. **PBAC comment:** Section 100 (Highly Specialised Drug Program) for consistency with the recommended restriction of riociguat for PAH may be more appropriate (para 2.2).	Section 100 HSD listing requested. Eligibility criterion requiring a right arterial pressure of ≤8 mmHg was removed. **PBAC comment:** Removal of this criterion was appropriate (para 2.2). **PBAC comment**: Assessment of operability can be subjective and a broader interpretation rather than strictly surgically inaccessible CTEPH may be applied. The PSCR (p4) proposed that adjudication by a local expert PEA centre be considered (para 2.3). **PBAC comment:** Requirement to have failed vasodilators appears to inappropriately require the use of inferior or unsubstantiated treatments prior to riociguat (para 2.3).	Requirement for inoperability to be assessed by a PEA centre. Eligibility criterion for initial treatment of inoperable CTEPH to include: - RHC demonstrating PVR of >300 dyn*sec*cm^{-5} ≥90 days after start of full anticoagulation, AND – PAPmean >25 mmHg, OR – Right ventricular function assessed by echocardiography demonstrating right ventricular dysfunction. For persistent CTEPH, as for inoperable but no requirement for PAPmean. Requirement to have failed to respond to ≥ 6 or more weeks of vasodilator treatment was removed from the requested restriction.

	November 2014 submission	July 2015 re-submission	March 2016 re-submission
Effective price	Initial (42 tablet pack): $[redacted]; Continuing (84 tablet pack): $[redacted] **PBAC comment:** Effective price is the same as the PBAC recommended price of riociguat for the treatment of PAH (para 6.26).	No change from November 2014: Initial (42 tablet pack): $[redacted]; Continuing (84 tablet pack): $[redacted]. The effective price of the 84 tablet pack was reduced in the pre-PBAC response by [redacted]% to $[redacted].	Initial (42 tablet pack): $[redacted]; Continuing (84 tablet pack): $[redacted] A [redacted]% reduction in the effective price for the initial and continuing packs was offered from the recommended price of riociguat for the treatment of PAH.
Main comparator	Placebo **PBAC comment:** Placebo is the appropriate comparator; in clinical practice, PAH treatments such as bosentan and sildenafil may be used off-label (para 7.2).	Same as November 2014: placebo. Due to the current off label use of pulmonary hypertension specific therapies, an indirect comparison of riociguat with bosentan and sildenafil was presented.	Same as July 2015.
Clinical evidence	CHEST-1 (n=261): randomised, double blind trial comparing riociguat and placebo over 16 weeks CHEST-2 (n=182): supplementary long term extension study	No changes to the direct evidence, however the re-submission presented a literature review investigating the relationship between the 6MWD, WHO FC and OS; additional post-hoc analyses exploring the predictive nature of WHO FC and OS, as well as indirect comparisons: riociguat vs. bosentan; riociguat vs sildenafil; and an updated PSUR. **PBAC comment:** The PBAC considered that while changes in the 6MWD are likely to predict a survival gain the magnitude of the effect was not certain, and that the claim of a relationship between changes in WHO functional class and survival was not adequately supported and could not be quantified (para 7.5).	While no new clinical trial evidence was presented, the re-submission found two additional citations in the literature review investigating the relationship between the 6MWD, WHO FC and OS. This didn't change the conclusion regarding this relationship from the July 2015 re-submission.
Key efficacy data	CHEST-1: riociguat vs placebo - LSMD for change in 6MWD (metres): 45.69, (95% CI: 24.74, 66.63) - Improvement of ≥1 WHO functional class: RR = 2.2, (95% CI: 1.28, 3.80)	Direct comparison: riociguat vs placebo - no change from November 2014.	Direct comparison: riociguat vs placebo – no change from July 2015.
Key safety data	CHEST-1: riociguat vs placebo: - Statistically significant differences observed for dizziness (RD% = 11.6, 95% CI: 5.1, 18.2) and hypotension (RD% = 8.1, 95% CI: 2.3, 13.9).	Direct comparison: riociguat vs placebo - no change from November 2014. PSUR: Updated PSUR data provided.	Direct comparison: riociguat vs placebo – change from July 2015. PSUR: An updated PSUR was provided.
Clinical claim	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 **PBAC comment:** The PBAC did not accept this (para 7.4), noting superiority of riociguat for comparative effectiveness using change in 6MWD from baseline and inferiority to placebo for comparative safety (para 6.15).	Riociguat is superior to placebo for the treatment of CTEPH and non-inferior for safety. **PBAC comment:** The PBAC considered that superior comparative effectiveness was a reasonable claim for improvements in 6MWD and WHO functional class (paragraph 6.20) and that the claim of non-inferior comparative safety was not adequately supported (para 6.19).	Riociguat is superior to placebo for the treatment of CTEPH and although riociguat is associated with a higher incidence of dizziness and hypotension and inferior to placebo, the risk benefit profile remains very favourable.

	November 2014 submission	July 2015 re-submission	March 2016 re-submission
Economic analysis	None presented **PBAC comment:** At this time, the value for money of riociguat treatment for patients with CTEPH, relative to placebo, is unknown (para 7.5).	Cost utility analysis for the comparison of riociguat and placebo presented (base case corrected^ ICER = $45,000-$75,000). Pre-PBAC response: revised with gradual reduction in bosentan substitution and reduced effective price: $45,000-$75,000 overall ($45,000-$75,000 for surgical and $15,000-$45,000 for non-surgical patients). **PBAC comment:** There was a disconnect between the model and the clinical data and uncertainty regarding the survival gain (para 7.7). There were inadequate patient numbers to reliably determine transition probabilities and utilities associated with WHO functional class IV, and inadequate justification that the costs of bosentan will apply for 30% of placebo patients and ongoing treatment benefits for riociguat over 15 years. The use of placebo survival estimates based on a non-surgical cohort from Condliffe 2008 overestimated incremental difference in survival (para 7.8).	Cost utility analysis for riociguat versus placebo (with 74% use of off-label therapies) presented in the re-submission. Model based on extrapolated survival with inoperable and persistent PH after surgery modelled in separate cohorts. Base case ICER in re-submission of $15,000-$45,000; $15,000-$45,000 for inoperable patients and $45,000-$75,000 for persistent patients. Corrected base case ICER* $45,000-$75,000; $45,000-$75,000 for inoperable and $45,000-$75,000 for persistent patients.
Estimated net cost to government	Submission: Year 1: less than $10 million, Year 5: $10-$20 million. Total Years 1-5: $30-$60 million Pre-PBAC response: Year 1: less than $10 million; Year 5: less than $10 million. **PBAC comment:** The pre-PBAC response patient numbers and financial estimates were updated in line with the DUSC advice (para 6.25).	While revisions from the pre-PBAC response were carried through to the re-submission's financial estimates, additional cost off-sets associated with an assumed reduction in bosentan off-label use were included in the financial estimates: and were revised in the pre-PBAC response to Year 1:less than $10 million; Year 5: less than $10 million. Total Years 1-5: $30-$60 million. **PBAC comment:** Savings from reduced use of bosentan may not be realised (para 7.9).	Additional cost off-sets due to an expected 74% substitution of bosentan, ambrisentan, sildenafil and tadalafil in Year 1, with a gradual reduction in switches to zero by Year 5. Year 1: less than $10 million; Year 5:less than $10 million; Total Years 1-5: $10-$20 million.
PBAC outcome	Reject	Reject	NA

^ A minor calculation error associated with the calculation of placebo transition probabilities for WHO functional class II to III was located during the evaluation. *Updated during the evaluation to include 6 monthly RHC for patients in WHO FC II.
6MWD = 6 minute walk distance test; CTEPH = chronic thromboembolic pulmonary hypertension; ECHO = echocardiogram; LSMD = least square mean difference; MCID = minimal clinically important difference; MD = mean difference; NA = not applicable; PEA = pulmonary endarterectomy; PAH = pulmonary arterial hypertension; OS = overall survival; PSUR = periodic safety update report; RAP = right atrial pressure; RHC = right heart catheterisation; RD = risk difference; RR = relative risk; PSCR = pre subcommittee response; FC = functional class; OS = overall survival; para = paragraph. Source: constructed during the evaluation. Paragraph references refer to the November 2014 PSD or July 2015 PSD, depending on the respective column the reference is made in relation to, for riociguat.

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

4 Clinical place for the proposed therapy

4.1 CTEPH (PH Group 4) is a progressive disease where pulmonary vascular resistance (PVR) increases progressively, ultimately resulting in right heart failure and death.

4.2 PEA is a potentially curative surgical intervention for CTEPH. The re-submission proposed that riociguat be used for patients who cannot receive PEA (inoperable) or those who have persistent CTEPH after surgery, replacing either no treatment (placebo) or medical therapies. Currently, medical therapy may include the use of endothelin receptor antagonists (ERAs) such as bosentan and ambrisentan, and phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil and tadalafil, although none of these drugs are PBS-listed for CTEPH.

5 Comparator

5.1 As in the November 2014 submission and the July 2015 re-submission, the re-submission nominated placebo as the main comparator. The PBAC previously accepted placebo as the main comparator, although noted that in clinical practice, other PAH treatments such as bosentan and sildenafil may be used off-label (November 2014 riociguat PSD, paragraph 7.2). An indirect comparison of riociguat to bosentan and a separate comparison to sildenafil were provided in the July 2015 re-submission. Given the re-submission's assertion that 74% of inoperable CTEPH or persistent CTEPH after PEA patients are taking either an ERA or a PDE-5 inhibitor, the evaluation considered that it may be reasonable to consider bosentan or sildenafil as an alternate comparator. The re-submission raised this possibility, although there was no comparative economic evidence against such an alternate comparator provided.

5.2 The Pre-Sub-Committee Response (PSCR, p1) argued that "…neither bosentan nor sildenafil have the clinical evidence to support the use in the treatment of patients with CTEPH, despite being used off-label extensively as demonstrated in the current re-submission. Riociguat is the first and only therapy with a demonstrated clinical benefit in the proposed patient population, and a placebo is therefore the relevant main comparator. It follows that with the exception of including the drug cost of both therapies in the economic analysis, there is no clinical basis to support a comparative economic evidence assessment, especially since the neither [sic] clinical effectiveness nor the cost-effectiveness of these treatments in CTEPH has been established or assessed by the TGA and PBAC."

5.3 The ESC agreed with the PSCR that placebo was the appropriate comparator. However, the ESC did not agree that there should be an exception for including the drug cost of off-label therapies in the base case economic analysis (see paragraph 6.26). Rather, the ESC considered that if the costs of these drugs were to be included it should be in sensitivity analyses.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from an individual (1) via the Consumer Comments facility on the PBS website. The comment indicated that the individual would like to have increased mobility, fewer side effects, better quality of life and a decrease in progression of the disease.

Clinical trials

6.7 As with the November 2014 submission and the July 2015 re-submission, the re-submission was based on one head-to-head trial (CHEST-1, n=261) comparing riociguat to placebo and one supplementary extension study (CHEST-2, n=237 enrolled). The re-submission did not present any new clinical trial evidence. The re-submission presented an updated periodic safety update report and a revised clinical claim.

6.8 Details of the trials presented in the re-submission are unchanged from the July 2015 re-submission, with the exception of the addition of two studies published in 2015, and are summarised in the following table.

Table 2: Trials and associated reports presented in the re-submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
CHEST-1	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).	30th Oct 2012
	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.	*New England Journal of Medicine.* 2013; 369(4):319-29
	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.	*American Journal of Respiratory & Critical Care Medicine.* 2012; 185: A2370
	D'Armini A, Ghofrani HA, Kim NH, Mayer E, Simonneau G, Wilkins MR, Pulido T, Fritsch A, Davie N, 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.	*European Respiratory Journal.* 2013; 42. Suppl 57, P2598
	Ghofrani HA, Grimminger F, Hoeper MM, Nick K, Meyer E, Neuser D, 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).	*Chest* 2012; 142 (4_MeetingAbstracts) :1023A
	Ghofrani HA, Grimminger F, Hoeper MM, Kim NH, Mayer E, Simonneau G, Sikirica M, Fritsch A, Davie N, Luong B, Wilkins MR. Impact of riociguat on health-related quality of life (HRQoL) in patients with chronic thromboembolic pulmonary hypertension (CTEPH).	*European Respiratory Journal.* 2013; 42. Suppl 57, P3418
	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.	*European Heart Journal.* 2013; 34 (suppl 1): 187
	Marra AM, Egenlauf B, Ehlken N, Fischer C, et al. Change of right heart size and function by long-term therapy with riociguat in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.	*International Journal of Cardiology 2015; 195, 19-26*

Extension study		
CHEST-2	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).	3rd May 2012
	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.	*Chest.* 2013; 144 (4_MeetingAbstracts) :1023A
	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.	*Chest.* 2014; 145 (3_MeetingAbstracts) :535B
	Simonneau G, D'Armini AM, Ghofrani HA, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: A long-term extension study (CHEST-2).	*European Respiratory Journal 2015; 45, 1293-1302.*
	Simonneau G, D'Armini AM, Ghofrani HA, Grimminger F, et al. Late breaking abstract: Riociguat for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH): 2-year results from the CHEST-2 long term extension.	*European Respiratory Journal 2014; 44: Suppl 58.*

Source: Table B.2-2, p41-42 of the re-submission.

6.9 The key features of the CHEST-1 trial and the CHEST-2 extension study are summarised in the following table.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome	Use in modelled evaluation
Riociguat vs placebo						
CHEST-1	261	R, DB, 16 weeks	Low	Inoperable and persistent CTEPH	6MWD, WHO FC	Parametric extrapolations for change in WHO FC (first cycle); initial distribution of patients by WHO FC; EQ-5D; transition probabilities for discontinuation of treatment; parametric extrapolations for overall survival for riociguat
CHEST-2	237*	SB titration for 8 weeks, LTE, 4.8 years**	Low	Inoperable and persistent CTEPH	6MWD, WHO FC	Parametric extrapolations for overall survival for riociguat; parametric extrapolations for change in WHO FC (subsequent cycles)

6MWD = 6-minute walking distance test; CTEPH = chronic thromboembolic pulmonary hypertension; DB = double blind; FC = functional class; R = randomised; SB = single blind; LTE = long-term extension. Note: *number of enrolled patients; **maximum period of follow-up. Source: compiled during the evaluation.

Comparative effectiveness

6.10 At the November 2014 meeting, the PBAC noted the statistical significance of treatment effect in terms of the primary endpoint change in 6MWD favouring riociguat over placebo. The Committee further noted that the mean difference (45.7 metres) was within the minimal clinically important difference (MCID) of 35 to 50 metres it had previously accepted (November 2014 PSD, paragraph 7.3). Key results from the pivotal trial (CHEST-1) are unchanged from the July 2015 re-submission, and are summarised in the following table.

Table 4: Summary of key results from CHEST-1

	Riociguat (n=173)	Placebo (n=88)
6MWD, metres		
Baseline, mean (SD)	342.3 (81.9)	356.0 (74.7)
Change from baseline at 16 weeks	38.9 (79.3)	-5.5 (84.3)
Least square mean difference (95% CI)	**45.69 (24.74, 66.63)**	
Change in WHO functional class (baseline to 16 weeks)		
Improvement of ≥1 class (95% CI)	**RR* = 2.20 (1.28, 3.80)**	
Stable or improvement of ≥ 1 class (95% CI)	RR* = 1.02 (0.95, 1.09)	

*Relative risks calculated during the evaluation using StatsDirect Version 2.7.9. **Values in bold represent statistically significant differences observed between treatment groups.** 6MWD = 6-minute walking distance test; RR = relative risk; SD = standard deviation; 95%CI = 95% confidence interval. Source: Table B.6-1, p99; Table B.6-6, p107 of the re-submission.

Comparative harms

6.11 The comparative harms for riociguat versus placebo were unchanged from the July 2015 re-submission and are summarised as follows: in the CHEST-1 trial there was a statistically significant increased incidence of dizziness (RD% 11.6, 95% CI: 5.1, 18.2) and hypotension (RD%: 8.1, 95% CI: 2.3, 13.9) in the riociguat treatment arm compared with placebo. Additional data presented in the re-submission in the form of an updated periodic safety update report did not suggest any new safety concerns.

Benefits/harms

6.12 The comparative benefits and harms for riociguat versus placebo were unchanged from the July 2015 re-submission and are summarised in the following table.

Table 5: Summary of comparative benefits and harms for riociguat and placebo (CHEST-1)

	Riociguat			Placebo			LSMD: Riociguat vs. placebo (95% CI)
	n	Mean Δ baseline	SD	n	Mean Δ baseline	SD	
Benefits							
Change in 6MWD, metres							
CHEST-1	173	38.9	79.3	88	-5.5	84.3	45.7 (24.7, 66.6)

	Riociguat	Placebo	RR (95% CI)	Event rate/100 patients*		RD% (95% CI)
				Riociguat	Placebo	
Improvement by ≥1 WHO Functional class						
CHEST-1	57/173	13/87	2.2 (1.3, 3.8)	32.9	14.9	18.0 (7.7, 28.3)
Harms						
Dizziness	26/173	3/88	4.4 (1.4, 14.2)	15.0	3.4	11.6 (5.1, 18.2)
Hypotension	14/173	0/88	NC	8.1	0.0	8.1 (2.3, 13.9)

*CHEST-1 trial duration = 16 weeks. Abbreviations: 6MWD = 6-minute walking distance test; LSMD = least square mean difference; NC = not calculable; SD = standard deviation; RD = risk difference; RR = risk ratio; CI = confidence interval. Source: p117 of the re-submission

6.13 On the basis of the direct evidence presented by the re-submission, treatment with riociguat in comparison to placebo over 16 weeks resulted in:

- An average increase of 46 metres in the distance able to be walked in 6 minutes. By comparison, participants were able to walk approximately 350 metres in 6 minutes at the beginning of the trial.

6.14 On the basis of the direct evidence presented by the re-submission, every 100 patients treated with riociguat in comparison to placebo resulted in:

- Approximately 18 additional patients with an improvement by ≥1 WHO functional class over 16 weeks.
- Approximately 12 additional patients with dizziness over 16 weeks.
- Approximately 8 additional patients with hypotension over 16 weeks.

Clinical claim

6.15 At the July 2015 meeting, the PBAC noted that the re-submission did not adequately justify a claim of non-inferiority in regard to comparative safety (July 2015 PSD, paragraph 6.17). The re-submission updated the clinical claim (p139), concluding that riociguat is superior to placebo for the treatment of CTEPH and although riociguat is associated with a higher incidence of dizziness and hypotension and inferior to placebo, the risk benefit profile remains very favourable. Overall, riociguat is considered to be inferior compared with placebo in regard to safety. The clinical claim presented did not unequivocally state this.

6.16 The ESC noted the statistically significant treatment effect in 6MWD and WHO functional class associated with riociguat (compared with placebo). The ESC also noted that riociguat is inferior to placebo with regard to safety.

6.17 The PBAC considered that the claim of superior comparative effectiveness, with regards to improvement in 6MWD and WHO functional class, was reasonable.

6.18 The PBAC considered that a claim of inferior comparative safety, with regards to a higher incidence of dizziness and hypotension was reasonable.

Economic analysis

6.19 The re-submission presented a modelled cost utility analysis. The economic model differed from the model presented in the July 2015 re-submission in that survival was modelled on the basis of overall survival rather than being dependent upon changes in WHO functional class, and the costs and outcomes associated with the treatment of patients with inoperable CTEPH and those with persistent CTEPH after surgery were evaluated as separate cohorts, rather than as a single cohort.

Table 6: Summary of model structure and rationale

Component	Summary			
Time horizon	15 years in the model base case versus 16 weeks in the head to head trial (CHEST-1). A maximum of 4.8 years follow-up was available for riociguat treated patients (CHEST-2).			
Outcomes	Cost/improvement of ≥1 WHO FC, Cost/LYG, Cost/QALY (trial based EQ-5D utilities)			
Methods used to generate results	A partitioned survival model comprising four health states: WHO FC health states (II, III, IV) and death: patients enter the model in either WHO FC II, III or IV according to the observed baseline distribution of patients in the CHEST-1 trial. With each cycle, patients may have a stepwise transition to a better/worse FC health state, remain stable or transition to the self-absorbing death health state at any time. Probability of death was modelled by exponential extrapolation. It was assumed that placebo patients could either improve or worsen in WHO FC in the first cycle. Subsequent to the first cycle, placebo patients were only permitted to have a worsening of WHO FC. It was assumed that for riociguat, that there were no functional class improvements from WHO FC IV to III.			
Health states	WHO FC II, III and IV and death			
Cycle length	First cycle: 112 days; subsequent cycles: 122 days; half cycle correction applied			
Transition probabilities		**WHO FC: deterioration (II to III, III to IV) & improvement (IV to III and III to II)**		**Death**
		First cycle	**Subsequent cycles**	
	Riociguat	CHEST-1: Log-normal extrapolation	CHEST-2: Log-normal extrapolation*	CHEST-1 & 2 (dataset 1): Exponential extrapolation
	Placebo		CHEST-1: Log-normal extrapolation^	Inoperable: Condliffe 2008 (non-surgical CTEPH cohort) diagnosed from 2003: HR = 3.52 Persistent: Condliffe 2008 (all surgical cohort) : HR=1.38
	Probability of treatment discontinuation: CHEST-1			

*Following the first cycle, the re-submission assumes no functional class improvement from WHO FC IV to III for riociguat treated patients. ^Following the first cycle, the re-submission assumed no functional class improvements for placebo treated patients. FC = functional class; HR = hazard ratio; LYG = life years gained; QALY = quality adjusted life year; CTEPH = chronic thromboembolic pulmonary hypertension. Source: compiled during the evaluation.

Table 7: Key drivers of the model

Description	Method/Value	Impact
Placebo survival extrapolation	Constant hazards approach derived from Condliffe 2008 (non-surgical CTEPH cohort): HR = 3.52; (all surgical cohort): HR = 1.38	High, favours riociguat
Off-label therapies	Assumption of 74% use of off-label therapies for placebo patients	High, favours riociguat
Time horizon	15 years	Moderate, favours riociguat

CTEPH = chronic thromboembolic pulmonary hypertension; FCTP = functional class transition probability; HR = hazard ratio.
Source: compiled during the evaluation.

6.20 The ESC considered that the reliability of the economic model was compromised by the following factors:

- Persistence of treatment benefits for riociguat throughout the 15-year timeframe of the economic model. Although the CHEST-2 extension study provided a maximum of 4.8 years of follow-up for riociguat treated patients, there was inadequate trial based evidence (16 weeks) to reliably calculate placebo transition probabilities for overall survival or for WHO functional class. In addition, the assumption of ongoing survival benefits for riociguat was an optimistic interpretation of the evidence considering the observational dataset used to inform placebo survival (refer below). A more conservative approach would have been the use of placebo based transition probabilities following the median duration of treatment for the March 2014 cut-off from CHEST-2.
    - The PSCR (p2) argued that an ongoing survival benefit for riociguat is likely given that patients must continue to receive treatment benefit for continued access to riociguat on the PBS. The ESC considered that there is no clinical evidence that the incremental benefit will remain the same over time.
    - The PSCR (p2) further argued that the more conservative approach proposed by the evaluation was not reasonable as it assumed that all treatment benefit dissipates immediately. The ESC reconfirmed that this conservative approach, given the absence of any evidence of the continuation of a benefit beyond the treatment period, would have been more appropriate than assuming the benefit would remain unchanged.
- The assumption of a constant hazard ratio and non-convergence of the survival curves at 15 years. This overestimates the benefit of riociguat.
    - The PSCR (p2) argued that the difference in survival between the treatment groups at 15 years is small and has a negligible effect on overestimation of the survival benefit.
- The high proportion of off-label therapy use (74%) assumed in the model was based on data obtained from the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ) registry. It is not clear whether the PHSANZ registry data was representative of the proposed PBS population for riociguat. The evaluation considered that it is more likely that patients will be included on a registry if they have received some form of active treatment and that the registry had a much smaller proportion of inoperable CTEPH patients (34/235 = 14%) than the submission assumed will be included in the PBS population (74% inoperable versus 26% persistent following surgery). In addition, the registry captures patients from New Zealand who may have different patterns of use of these therapies. Accordingly, the evaluation considered that it is likely that the proportion of off-label use of ERAs and PDE-5 inhibitors is substantially lower than 74%.

  - The PSCR (p3) stated that information on the proportion of New Zealand patients in the PHSANZ registry has been requested and that this will be provided to the PBAC when it becomes available. The PSCR stated that the risk of bias from the inclusion of New Zealand patients in the registry is likely to be low since only two centres out of 18 that provide data for the registry are New Zealand centres. The PSCR (p3) further argued that "the distribution of patients with inoperable and those with persistent CTEPH after surgery does not impact on whether these patients are treated or not, nor the types of treatments that are being used".
- Placebo extrapolations of survival are likely to be underestimated in the economic model with the Condliffe 2008 survival estimates not fully representing contemporary patients. The Condliffe historical cohort appear to have more severe disease and are not similar to the patients being considered, for example with respect to the proportion of patients predicted in the re-submission to be taking ERA or PDE-5 inhibitors.
  - The PSCR indicated that with 90% of non-surgical patients treated with an ERA, PDE-5 inhibitor or prostanoid therapy, survival for placebo patients is unlikely to have improved from that estimated using Condliffe 2008. The ESC noted that there is no evidence of a benefit of treatment with the off-label therapies in any case, as stated by the PSCR (p1).
- Inadequate patient numbers (n≤10) to reliably determine transition probabilities and utilities associated with WHO functional class IV.
- The ESC noted that while it was appropriate that life years gained was modelled on the basis of overall survival instead of WHO functional class, data against this outcome was not provided in Section B of the submission.

6.21 During the evaluation, the economic model was adjusted to include RHC tests for patients in WHO functional class II every 6 months, as required for continuing treatment under the requested restriction. The PSCR argued that this was inappropriate as RHC is not a mandatory test to be performed every 6 months and that ECHO can be used instead. The ESC considered that while ECHO is an alternate test listed in the proposed restriction, it is only an alternative test for patients in whom RHC cannot be justified on clinical grounds. The PSCR noted the impact on the ICER is marginal in any case.

6.22 Results for the economic evaluation, presented in the table below, incorporate the cost for the RHC tests.

Table 8: Results of the stepped economic evaluation

Step and component	Riociguat			Placebo			Increment		
Step 1: trial based economic evaluation (16 weeks)									
Costs*	$ [redacted]			$85.55			$ [redacted]		
Improvement of ≥1 WHO functional class	Risk difference = 0.18						NNT = 5.56		
Incremental cost/improvement of ≥1 WHO functional class							$ [redacted]		
Step 2: modelled economic evaluation: extrapolation to 15 years									
Costs*	$ [redacted]			$42.78			$ [redacted]		
LYG	5.96			5.03			0.93		
Incremental cost/LYG							$ [redacted]		
Step 3: modelled economic evaluation: all resource use									
	Inoperable	Persistent	Total	Inoperable	Persistent	Total	Inoperable	Persistent	Total**
Costs	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]
LYG	5.89	6.16	5.96	4.74	5.82	5.03	1.15	0.34	0.93
Incremental cost/LYG							$ [redacted]	$ [redacted]	$ [redacted]
Step 4: modelled economic evaluation: inclusion of utilities									
	Inoperable	Persistent	Total	Inoperable	Persistent	Total	Inoperable	Persistent	Total
Costs	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]
QALY	3.80	4.28	3.93	2.95	3.81	3.18	0.85	0.47	0.75
Incremental cost/QALY							**$** [redacted]	**$** [redacted]	**$** [redacted]

Note: The costs in steps 3 and 4 were updated during the evaluation to include 6 monthly RHC tests for patients in WHO FC II. *drug only plus dose titration costs and excluding off-label therapies. **assuming weighting of costs and outcomes according to use in clinical practice of 73% inoperable and 27% persistent. NNT = number needed to treat; LYG = life years gained; QALY = quality adjusted life year. Source: Table D.5-1, D.5-2, D.5-3, and D.5-4, pp243-250 of the re-submission.

The redacted table shows ICERs in the range of $45,000/QALY - $75,000/QALY.

6.23 The ICER, of $45,000 - $75,000 per QALY saved, was similar to that estimated in the July 2015 pre-PBAC response of $45,000 - $75,000. The base case ICER presented in the submission (which did not incorporate the cost for RHC tests) was $15,000 - $45,000 per QALY saved.

6.24 The re-submission calculated the disutility associated with treatment emergent adverse events (dizziness, headache and hypotension) to be 0.0467. The re-submission stated that it did not include this disutility in the base case to avoid double counting. The evaluation considered, however, that the disutility for these events for riociguat treated patients should be included in the base case of the economic evaluation. The evaluation stated that since treatment specific values were not used in the economic evaluation, the utility scores by WHO functional class (being pooled and not treatment specific values) only partially capture the disutility associated with riociguat. Including this disutility resulted in an ICER of $45,000-$75,000 per QALY saved ($45,000-$75,000 for inoperable CTEPH and $75,000 - $105,000 for persistent PH after PEA).

- The PSCR (p4) agreed that it would have been more appropriate to use treatment specific utility values (mean of the baseline and last visit values) and notes that the ICER decreases when these utility values are used. The PSCR stated that due to high stratification the treatment and cohort specific utilities were derived from a reduced number of observations. The PSCR therefore presents an alternate approach using treatment specific utility values for the ITT population that were

not stratified by operability status. The PSCR calculated that the ICER improved from $45,000/QALY - $75,000/QALY to $15,000/QALY - $45,000/QALY using the approach in the commentary, and that it further improves to $15,000/QALY - $45,000/QALY using the alternate approach. The ESC was unable to verify these alternate calculations of the ICER.

- The PSCR correctly acknowledged that any disutility from treatment emergent adverse events on 'active' placebo would not have been captured using treatment specific utility values since the CHEST-1 trial evaluated true placebo. However, the PSCR incorrectly states this biases the results against riociguat when the reverse is true.

6.25 Overall, riociguat appeared to be more cost-effective for the treatment of patients with inoperable CTEPH: the base case ICER without disutility included was $45,000-$75,000 for inoperable patients versus $45,000-$75,000 for patients with persistent CTEPH after PEA. The re-submission stated (p247) that if it was assumed that riociguat offers no incremental treatment benefit for patients with persistent/recurrent pulmonary hypertension after surgery, "the maximum cost of treatment with riociguat should be the same as that with treatment with off-label therapies. The cost of off-label therapies is approximately 32% lower than that with riociguat at the currently proposed cost-effective price specifically within this subgroup. In the event that a 'cost-minimisation analysis' approach is adopted for patients with persistent/recurrent pulmonary hypertension, the cost of riociguat per day would be $[redacted] for this sub-group representing 27% of total cohort". A lower cost-minimised price compared with off-label therapies may be appropriate for this patient cohort. It is not clear however, what that price should be, as the cost-effectiveness of off-label therapies for the treatment of CTEPH has not yet been determined. The ESC considered that applying a cost minimisation approach against the off-label therapies for persistent CTEPH patients following surgery would be inappropriate given that there is no clinical evidence to support their use in the treatment of patients with CTEPH.

6.26 While a significant treatment effect was predicted by the economic model, the ESC considered that the ICER was underestimated by the re-submission due to:

- the assumption of ongoing treatment benefits for riociguat across the 15-year duration of the model;
- the derivation of placebo survival from cohorts that may underestimate survival (Condliffe 2008), see paragraph 6.20 above; and
- the assumption that 74% of placebo patients will receive treatment with an ERA or PDE-5 inhibitor. In particular, the ESC considered that the inclusion of the costs of off-label therapies in the base case was not appropriate given that placebo is the comparator of interest. In this regard, the ESC noted that the base case ICER increased to $75,000/QALY - $105,000/QALY with the cost of off-label drugs removed.

6.27 In addition to the scenario of removing the cost of off-label medications, various other parameters were tested in the sensitivity analysis and the ICER was most sensitive to the inclusion of a disutility value for adverse events of riociguat (ICER increased to $45,000/QALY - $75,000/QALY for a disutility of 0.0467), the timeframe of the model (ICER increased to $75,000/QALY - $105,000/QALY for a 5-year model), and the 95% confidence intervals for placebo mortality (ICER increased to $75,000/QALY - $105,000/QALY for the lower 95% CI).

6.28 The pre-PBAC response (p3) presented new ICERs on the basis of a new price (effective AEMP of $[redacted] for the 84 tablet pack) under various scenarios (see the following table).

Table 9: Revised base case and sensitivity analyses

	Riociguat		Placebo		$/QALY
	Cost ($)	QALY's	Cost ($)	QALY's	
Submission base case	$[redacted]	3.93	$[redacted]	3.18	$[redacted]
Submission base case + RHC	$[redacted]	3.93	$[redacted]	3.18	$[redacted]
Revised base case with pre-PBAC response price offer					
Revised base case	$[redacted]	3.93	$[redacted]	3.18	$[redacted]
Revised base case + 50% off-label	$[redacted]	3.93	$[redacted]	3.18	$[redacted]
Revised base case + 50% off-label + RHC	$[redacted]	3.93	$[redacted]	3.18	$[redacted]
Revised base case + Treatment specific utility + RHC	$[redacted]	3.85	$[redacted]	2.86	$[redacted]
Revised base case + Treatment specific utility + RHC + 50% off-label	$[redacted]	3.85	$[redacted]	2.86	$[redacted]

Source: Pre-PBAC response and calculated

The redacted table above shows ICERs in the range of:

- Revised base case: $15,000/QALY - $45,000/QALY
- Revised base case + 50% off-label: $45,000/QALY - $75,000/QALY
- Revised base case + 50% off-label + RHC: $45,000/QALY - $75,000/QALY
- Revised base case + Treatment specific utility + RHC: $15,000/QALY - $45,000/QALY
- Revised base case + Treatment specific utility + RHC + 50% off-label: $15,000/QALY - $45,000/QALY

6.29 The PBAC agreed with the ESC that the reliability of the model was uncertain due to the issues raised in paragraphs 6.20 and 6.26. The PBAC acknowledged the limitations in the available data and considered that the reduced price for the 84 tablet pack offered in the pre-PBAC response addressed some of this uncertainty. In this context, the PBAC considered that the most appropriate base case for decision making in this instance should include:

- the cost of RHC tests;
- some acknowledgement of the use of off-label drugs in the estimate of cost effectiveness (but less than 74% of placebo patients) due to the likely widespread use in this patient population;
- the original submission utilities which appeared to be more conservative (and noting that the ESC was unable to verify the treatment specific utilities used in the PSCR and pre-PBAC response).

The PBAC noted that the ICER for this scenario was estimated to be around $45,000 - $75,000 per QALY.

Drug cost/patient/year: $[redacted]

6.30 The estimated drug cost/patient/year was calculated from an expected compliance rate of 10 continuing treatment prescriptions per patient per year. This compliance rate was based on a 10% sample of Medicare data for bosentan utilisation (2010-2013). In October 2014, the DUSC considered that this was an appropriate approach for determining riociguat compliance. Given an effective price of $[redacted] per continuing prescription for all riociguat strengths, the cost/patient/year was estimated to be $[redacted].

6.31 Using the revised price offer in the pre-PBAC response (of $[redacted] per continuing prescription), the drug cost/patient/year was estimated to be $[redacted].

Estimated PBS usage & financial implications

6.32 This re-submission was not considered by DUSC.

6.33 The re-submission included additional cost offsets associated with an assumed reduction in bosentan, ambrisentan, sildenafil and tadalafil use; [redacted]% cost offset in Year 1 compared with [redacted]% cost offset for bosentan alone in Year 1 in the July 2015 re-submission. In line with the July 2015 pre-PBAC response, the re-submission assumed a gradual reduction in the number of patients switching rather than a constant rate of switching (July 2015 PSD, paragraph 6.35).

Table 10: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use and cost of riociguat					
Patients treated with riociguat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
July 2015 re-submission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost of riociguat to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated changes in the use and cost of bosentan, ambrisentan, sildenafil and tadalafil associated with the listing of riociguat					
Reduction in bosentan, ambrisentan, sildenafil and tadalafil patients*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net savings in bosentan, ambrisentan, sildenafil and tadalafil cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated net cost to PBS/RPBS					
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
July 2015 re-submission	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
July 2015 pre-PBAC response	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net savings in bosentan LFT costs to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total net cost to government	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
July 2015 re-submission	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
July 2015 pre-PBAC response	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

*Based on a 74% switch rate in year 1, 56% in year 2, 37% in year 3, 19% in year 4, and 0% in year 5. Compared to a 30% constant rate switch in 2015 re-submission and a gradual reduction in switches from 30% in year 1 to 0% in year 5 in the July 2015 pre-PBAC response. LFTs = liver function tests. Source: Tables E.2-1, E.2-5, E.3-2 –E.3-4, p264-269 of the re-submission, and Tables E.5-2, E.5-3, p271-272 of the re-submission

6.34 At year 5, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than $10 million (with no savings from off-label therapies assumed by year 5).

6.35 Although riociguat for the treatment of PAH received a positive recommendation at the March 2014 PBAC meeting, progression to PBS listing has not occurred. The DUSC considered that in this scenario, there would be considerable risk of use outside the CTEPH restriction for PAH, but if both indications were PBS listed this would not be an issue.

6.36 While the financial estimates continue to assume a considerable increase in the CTEPH diagnosis rate (75% over 5 years), it is likely that net costs to government have been underestimated due to the predicted bosentan, ambrisentan, sildenafil and tadalafil cost offsets. It is unlikely that the extent of bosentan, ambrisentan, sildenafil and tadalafil savings included in the re-submission's financial estimates will be realised, given that the majority of CTEPH patients are receiving treatment under compassionate use programs or being subsidised through private health funds. In this regard, it is worth noting that the net financial cost to the PBS/RPBS of riociguat was estimated to be $30-$60 million over the first 5 years of listing.

- The PSCR (p4) acknowledged that some patients may currently be treated through compassionate use programs, but there are no estimates available regarding the total number of patients. Given the practical limits on the number of patients that could be enrolled in these programs, the PSCR argued that the majority of patients are likely to have been inappropriately classified as having pulmonary arterial hypertension to receive PBS subsidised treatment.

6.37 Sensitivity analyses indicated that the financial estimates were most sensitive to the proportion of patients switching from PBS subsidised bosentan, ambrisentan, sildenafil and tadalafil, and to the CTEPH diagnosis rate. Reducing the switching rate by half resulted in costs that were 1.15 times greater over 5 years when compared to the base case. Assuming that the diagnosis rate increased by only 37.5% over 5 years, rather than by 75% resulted in an [redacted]% reduction in costs over 5 years when compared to the base case.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of riociguat, on the basis that it should be available only under special arrangements under Section 100 (Highly Specialised Drugs Programme) for the treatment of patients with inoperable CTEPH or persistent CTEPH subsequent to pulmonary endarterectomy under certain conditions (see recommended listing).

7.2 The PBAC previously accepted that placebo is the appropriate comparator in this place of therapy, while noting that other PAH treatments such as bosentan and sildenafil may be used off-label in clinical practice. The PBAC was satisfied that riociguat provides, for some patients, a significant improvement in efficacy over placebo.

7.3 The PBAC noted that the re-submission proposed that the requirement for assessment of operability be confirmed by a local expert PEA centre and that the initial and continuing response measurements appropriately included RHC, PAPmean, ECHO and 6MWT. The PBAC noted that the sponsor intends for riociguat

to be listed on the PBS for PAH (recommended in March 2014) at the same time as CTEPH. The restriction for PAH is yet to be finalised. The PBAC considered that the restrictions for the CTEPH and PAH indications are complex and will require consultation with the Restrictions Working Group.

7.4 The PBAC noted that as per the November 2014 and July 2015 submissions, the re-submission was based on one head-to-head trial (CHEST-1) comparing riociguat to placebo and one supplementary extension study (CHEST-2). The PBAC noted the mean difference in 6MWD of 45.7 metres for patients treated with riociguat, compared with placebo, was within the previously accepted MCID of 35 to 50 metres. The PBAC further noted the statistically significant improvement of at least one WHO functional class associated with riociguat, compared with placebo.

7.5 The PBAC noted the statistically significant increase in incidence of dizziness and hypotension in the riociguat treatment group, compared with placebo. In this regard, the PBAC considered that riociguat has inferior comparative safety to placebo. However, the PBAC considered that these adverse events would be unlikely to deter patients with inoperable CTEPH or persistent CTEPH following PEA without other treatment options from being treated with riociguat.

7.6 The resubmission addressed some of the PBAC's previous concerns with the model structure, including the previous disconnect between the clinical data (which was based on 6MWD) and the model (which was based on a relationship between WHO functional class and survival). In addition, the re-submission modelled patients with inoperable CTEPH and those with persistent CTEPH following surgery separately. The PBAC agreed with the ESC that the reliability of the model remained somewhat compromised by the factors discussed in paragraph 6.20. While noting the limitations in the available data, however, the PBAC considered that the most appropriate ICER for decision making may be around $45,000/QALY - $75,000/QALY (see paragraph 6.29). In the context of the clinical need for an effective treatment for this condition, the small patient population, the Authority Required (in-writing) continuation rule in the requested restriction, and the revised price offer in the pre-PBAC response, the PBAC pragmatically considered that the cost-effectiveness was acceptable enough to allow recommendation in this instance.

7.7 The PBAC noted the financial estimates will need to be revised to take into account the revised price offer in the pre-PBAC response. In addition, the financial estimates should reflect a reduced proportion of patients switching from off-label therapies given that the majority of patients are likely to be receiving treatment under compassionate use programs or being subsidised through private health funds (as opposed to the PBS).

7.8 The PBAC advised that riociguat is not suitable for prescribing by nurse practitioners.

7.9 The PBAC noted that the Early Supply Rule does not currently apply to Section 100 (Highly Specialised Drugs Programme) listings. The PBAC recommended that if the Early Supply Rule is applied to Section 100 listings in the future, it should not be applied to drugs listed for CTEPH and PAH given that patient status can rapidly deteriorate with these conditions.

7.10 The PBAC recommended under Section 101(3BA) of the *National Health Act 1953*,

that riociguat should not be treated as interchangeable on an individual patient basis with any other drugs or medicinal preparations.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item. Restriction to be finalised.

9 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.

10 Sponsor's Comment

Bayer welcomes the recommendation from the PBAC to list riociguat on the PBS and will continue to work with the Department to bring access to patients suffering from this rare and severe disease.