# 7.05 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. The 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

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Name, Restriction,  Manner of administration and form | Max.  Qty | №.of  Rpts | | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer | | |
| **Initial treatment** | | | | | | | |
| Riociguat  0.5mg, 1.0mg, 1.5mg, 2.0mg, 2.5mg tablets | 42 | 0 | $''''''''''''''''''''''' (Public hospital)  $'''''''''''''''''''''' (Private hospital)  $''''''''''''''''''''' (Effective price) | | Adempas® | | BN |
| **Continuing treatment** | | | | | | | |
| Riociguat  0.5mg, 1.0mg, 1.5mg, 2.0mg, 2.5mg tablets | 84 | 5 | $'''''''''''''''''''''' (Public hospital)  $'''''''''''''''''''''''(Private hospital)  $'''''''''''''''''''''' (Effective price) | | | Adempas® | BN |

|  |  |
| --- | --- |
| **Treatment phase: initial (new patients)** | |
| Severity | WHO Functional Class II-IV |
| Condition | Inoperable CTEPH or Persistent CTEPH subsequent to PEA. |
| Restriction | Authority required |
| Treatment criteria | Patients must have failed to respond to 6 or more weeks of appropriate vasodilator treatment unless intolerance or a contraindication to such treatment exists. |
| Clinical criteria | Initial PBS-subsidised treatment with riociguat of patients who have been assessed by a physician from a designated hospital to have:   1. WHO Functional Class II-IV inoperable CTEPH, as measured by RHC, or, where a RHC cannot be performed on clinical grounds, right ventricular function as assessed by ECHO; or 2. WHO Functional Class II-IV persistent CTEPH subsequent to PEA, as measured by RHC, or, where a RHC cannot be performed on clinical grounds, right ventricular function as assessed by ECHO.   Applications for authorisation must be in writing and must include:   1. two completed authority prescription forms; and 2. a completed Pulmonary Hypertension PBS Authority Application - Supporting Information form [www.medicareaustralia.gov.au] which includes results from the 3 tests below, where available: 3. RHC composite assessment; and 4. ECHO composite assessment; and 5. 6MWT; and 6. a signed patient acknowledgment form.   Details of prior vasodilator treatment, including the dose and duration of treatment, must be provided at the time of application. Where the patient has an adverse event to a vasodilator or where vasodilator treatment is contraindicated, details on the nature of the adverse event or contraindication according to the TGA-approved Product Information must also be provided with the application.  Where fewer than 3 tests (see requirement 2 above) are able to be performed on clinical grounds, a patient specific reason outlining why the particular test/s could not be conducted must be provided with the authority application [see Note for test requirements].  The maximum quantity authorised will be limited to provide sufficient supply for 2 weeks treatment, based on the dosage recommendations in the TGA-approved Product Information. A maximum of 3 subsequent authority prescriptions may be issued under this criterion. No repeats will be authorised for any of the authority prescription issued under this criterion. |
| **Treatment phase: continuing treatment (all patients)** | |
| Severity | WHO Functional Class II-IV |
| Condition | Inoperable CTEPH or Persistent CTEPH subsequent to PEA. |
| Restriction | Authority required |
| Clinical criteria | 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 [see Note for definition of response].  Applications for authorisation must be in writing and must include:   1. a completed authority prescription form; and 2. a completed Pulmonary Hypertension PBS Authority Application - Supporting Information form [www.medicareaustralia.gov.au] which includes results from the 3 tests below, where available: 3. RHC composite assessment; and 4. ECHO composite assessment; and 5. 6MWT.   The results of the same tests as conducted at baseline should be provided with each written continuing treatment application (i.e. every 6 months), except for patients who were able to undergo all 3 tests at baseline, and whose subsequent ECHO and 6MWT results demonstrate disease stability or improvement, in which case RHC can be omitted. In all other patients, where the same test(s) conducted at baseline cannot be performed for assessment of response on clinical grounds, a patient specific reason why the test(s) could not be conducted must be provided with the application.  The maximum quantity authorised will be limited to provide sufficient supply for 1 month of treatment, based on the dosage recommendations in the TGA-approved Product Information. A maximum of 5 repeats will be authorised.  Where fewer than 5 repeats are initially requested under this criterion, authority approvals for sufficient repeats to complete a maximum of 6 months of treatment may be requested by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday) |

Note: The re-submission did not provide the requested restriction in the standard table format; the information provided in the re-submission was placed into this format during the evaluation.

* 1. The re-submission has sought listing for riociguat on the basis of a cost utility analysis comparing riociguat and placebo.
  2. The re-submission amended the requested restriction, removing the eligibility criterion requiring a right arterial pressure (RAP) of ≤8 mmHg. This amendment was appropriate, given that the approved product information and eligibility criteria from the pivotal trial (CHEST-1) did not specify treatment on the basis of observed RAP. The effective price of $'''''''''''''''''''' for initial treatment and $''''''''''''''''''' for continuing treatment was unchanged in the re-submission.
  3. The re-submission indicated that the requested restriction was largely modelled on the restrictions currently used for pulmonary hypertension specific therapies. Although the PBAC previously indicated this may be appropriate (November 2014 riociguat public summary document (PSD), paragraph 2.2), there are a number of aspects in the authority criteria that would require further clarification due to differences associated with CTEPH (compared with pulmonary hypertension):
  + Initial and continuing treatment parameters: the re-submission did not specify initial or continuing response measurements for right heart catheterisation (RHC), echocardiogram (ECHO) or the 6 minute walking distance test (6MWD) that are relevant for inoperable CTEPH or persistent CTEPH patients.
  + Failed response to vasodilator treatment: this appears to necessitate prior treatment with vasodilators, which may include bosentan or sildenafil. Based on the re-submission’s claimed superiority for exercise capacity when compared with bosentan and inconclusive evidence for the use of sildenafil, the requested restriction would appear to inappropriately require the use of inferior or unsubstantiated treatments prior to riociguat. The PSCR proposed that the requirement for prior vasodilator therapy be removed from the requested restriction, given that there was no evidence to suggest differences in treatment response in this subset of the CTEPH population.
  + Guidance for the interpretation of inoperable CTEPH: it cannot be determined whether inoperable CTEPH should be interpreted within the context of strictly surgically inaccessible CTEPH. Given the subjectivity associated with the assessment of operability, a broader interpretation may be applied in clinical practice. Inoperability could result from imbalances within pulmonary vascular resistance (PVR) and accessible occlusions, PVR >1500 dyn s cm-5, age, co‑morbidities, presence of mild disease or personal choice. Acknowledging the complexity involved in the assessment of operability in CTEPH, the PSCR proposed that adjudication by a local expert PEA centre be considered as a potential criterion within the restriction.

1. Background
   1. Riociguat was approved for TGA registration for pulmonary arterial hypertension (PAH) and CTEPH in April 2014.
   2. The PBAC previously considered riociguat for the treatment of inoperable CTEPH or persistent CTEPH following PEA in November 2014. 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 WHO functional class changes and overall survival because of differences in the diseases and trial population characteristics (November 2014 riociguat PSD, paragraph 7.4).
   3. The PBAC concluded that an economic evaluation was the most appropriate option for determining cost effectiveness and the value for money of riociguat treatment for patients with CTEPH, relative to placebo, was unknown (November 2014 riociguat PSD, paragraph 7.5). This issue has been addressed in the re-submission with the presentation of a cost utility analysis for the comparison of riociguat and placebo (refer to economic analyses for further details and comments). Other relevant PBAC comments and changes in the re-submission are summarised in Attachment B.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

1. Clinical place for the proposed therapy
   1. CTEPH is a progressive disease where PVR increases progressively, ultimately resulting in right heart failure and death.
   2. PEA is a potentially curative surgical intervention for CTEPH. The re-submission proposes that riociguat be used for patients who cannot receive PEA (inoperable) or those who have persistent CTEPH following surgery, replacing either no treatment (placebo) or medical therapies. Currently, medical therapy may include the use of PAH drugs such as bosentan and sildenafil.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

1. Comparator
   1. As in the November 2014 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). The ESC considered that placebo was the appropriate comparator.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

1. Consideration of the evidence

## Sponsor hearing

* 1. There was no hearing for this item.

## Consumer comments

* 1. The PBAC noted and welcomed the input from individuals (12) and health care professionals (5) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with riociguat, including improved quality of life and functional capacity and improved life expectancy. It was noted that the cost of non-reimbursed riociguat currently limits patient access to the drug.

## Clinical trials

* 1. As with the November 2014 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=182). Changes to the evidence were presented in the re-submission, which included:
* a literature review investigating the relationship between the 6MWD, WHO functional class and overall survival;
* additional post-hoc analyses exploring the predictive nature of WHO functional class and overall survival;
* indirect comparisons of riociguat vs bosentan and riociguat vs sildenafil;
* an updated periodic safety update report; and
* a revised clinical claim.
  1. Details of the trials presented in the re-submission are provided in the following table.

Table 1: 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 |
| **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 |

Source: Table B.2-2, p34 of the re-submission.

* 1. The key features of the CHEST-1 trial are summarised in the following table.

Table 2: 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 |

Abbreviations: 6MWD = 6 minute walking distance test; CTEPH = chronic thromboembolic pulmonary hypertension; DB=double blind; FC = functional class; R=randomised. Source: compiled during the evaluation.

## Comparative effectiveness

* 1. 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 riociguat PSD, paragraph 7.3). Key results from the pivotal trial (CHEST-1) are presented in the table below.

Table 3: Summary of key results from CHEST-1

| 6MWD, metres | Riociguat (n=173) | Placebo (n=88) |
| --- | --- | --- |
| 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) | | *Riociguat (n=173)* | *Placebo (n=87)* |
| --- | --- | --- | --- |
| Improvement of ≥1 class | n (%) | 57 (32.9) | 13 (14.9) |
| *RR (95% CI)\** | 2.20 (1.28, 3.80) | |
| *NNT (95% CI)\** | 6 (4, 13) | |
| Stable or improvement of ≥ 1 class | n (%) | 164 (94.8) | 81 (93.1) |
| *RR (95% CI)\** | 1.02 (0.95, 1.09) | |
| *NNT (95% CI)\** | Not calculated – no statistically significant difference | |

\* Relative risk and number needed to treat calculated during the evaluation using StatsDirect Version 2.7.9. Values in bold represent statistically significant differences observed between treatment groups. Abbreviations: 6MWD = 6 minute walking distance test; NNT = number needed to treat; RR = relative risk; SD = standard deviation. Source: Table B.6-1, p 71; Table B.6-6, p78-79 of the re-submission.

* 1. For the indirect comparison of riociguat (CHEST-1, n=261) vs bosentan (Jais 2008, n=157), a statistically significant difference in favour of riociguat was observed for mean difference in 6MWD (42.3 metres, 95% CI: 9.6, 74.8).
  2. No formal indirect comparison of riociguat and sildenafil (Suntharalingam 2008, n=19) was presented in the re-submission. This was appropriate, given the small trial population, insufficient powering for the primary endpoint (change in 6MWD from baseline to week 12), disproportionate distribution of participants and the inconsistent reporting of results in Suntharalingam 2008.

## Comparative harms

* 1. 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 to placebo. Additional data in the periodic safety update report did not suggest any new safety concerns.

## Benefits/harms

* 1. A summary of the comparative benefits and harms for riociguat versus placebo is presented in the table below.

Table 4: Summary of comparative benefits and harms for riociguat and placebo (CHEST-1)

|  | **Riociguat** | | | | **Placebo** | | | | | **LSMD: Riociguat vs. placebo (95% CI)** | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **n** | **Mean ∆ baseline** | | **SD** | **n** | **Mean ∆ 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: page iv of the re-submission.

* 1. 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. At the beginning of the CHEST-1 trial, participants were able to walk approximately 350 metres in 6 minutes.
  2. On the basis of the direct evidence presented by the re-submission, every 100 patients treated with riociguat in comparison to placebo over 16 weeks resulted in approximately:
* 18 additional patients with an improvement by ≥1 WHO functional class.
* 12 additional patients with dizziness; and
* 8 additional patients with hypotension.

## Clinical claim

* 1. At the November 2014 meeting, the PBAC did not accept the previous submission’s claim of equivalence in comparative effectiveness and safety for riociguat in the PAH population and the proposed CTEPH population (PSD, paragraph 7.4). The re‑submission updated the clinical claim, concluding that riociguat is superior to placebo for the treatment of CTEPH and non-inferior for safety. Importantly, on the basis of post-hoc analyses presented in the original submission and in the re‑submission, it was claimed that changes in exercise capacity for patients with CTEPH also translated to a survival benefit. The evaluation and the ESC considered that while this claim may be appropriate in terms of the relationship between 6MWD and survival, the relationship between changes in WHO functional class and survival was not adequately supported:
* Relationship between 6MWD and survival: the PBAC previously 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 presented analyses (November 2014 riociguat PSD, paragraph 7.3). Although the re-submission’s presentation of additional observational evidence was supportive of the relationship between 6MWD and overall survival, it should be noted that long term survival in the economic model was based on changes in WHO functional class.
* Relationship between WHO functional class and survival: new post-hoc analyses investigating the relationship of changes in WHO functional class and overall survival did not indicate a significant association (HR=0.508, 95%CI: 0.215, 1.20) and inconsistent results were observed in the published literature. Consequently, the relationship between changes in WHO functional class and survival could not be definitively quantified.

* 1. The PSCR argued that a trend towards survival and decreasing WHO functional class was demonstrated in the post-hoc analyses and the lack of statistical significance was likely due to the limited number of available observations. The PSCR indicated that the modelling of overall survival based on deaths in each WHO functional class was pragmatic, given that this approach has been used in the modelling of pulmonary hypertension in the health economic literature. Furthermore, the PSCR noted that WHO functional class at baseline is a significant predictor of survival (HR=0.31 (95%CI 0.12-0.79)). The ESC considered it would expect that baseline WHO functional class is predictive of survival given that less sick people tend to live longer. However, the claimed clinical benefit related to improvements in WHO functional class from baseline.
  2. The ESC noted the statistically significant treatment effect in 6MWD associated with riociguat (compared with placebo) and that the PBAC previously considered that changes in the 6MWD are likely to predict a survival gain, but was not confident in the magnitude of the effect. The ESC considered the claim that changes in exercise capacity for patients with CTEPH translated to a survival benefit was supported in terms of 6MWD. However, the ESC considered that the claim of a relationship between improvements in WHO functional class and survival was not adequately supported and could not be quantified.
  3. While the re-submission acknowledged significant differences for dizziness, hypotension and headache[[1]](#footnote-1), the re-submission justified a non-inferiority claim with regard to comparative safety on the basis of:
* No treatment discontinuation attributable to dizziness, hypotension and headache. While this was indicative of acceptable tolerability, non-inferiority cannot be implied as this observation disregarded any on-treatment clinical impact.
* Incremental improvements for riociguat EQ-5D utilities compared with placebo from baseline to last visit (stratified by WHO functional class). The re-submission claimed this was indicative of no significant disutility associated with adverse events. The evaluation considered that this conclusion was unreasonable given the lack of specific EQ-5D analyses in patient groups impacted by dizziness, hypotension or headache.
  1. Overall, the re-submission did not adequately justify a claim of non-inferiority in regard to comparative safety. A conclusion of inferiority to placebo for comparative safety was noted by the PBAC in November 2014 (riociguat PSD, paragraph 6.15). The PSCR acknowledged that the significant increase in hypotension would be aligned with an inferior safety claim.
  2. The re-submission made the following clinical claims for the indirect comparisons:
* Riociguat vs bosentan: riociguat is superior to bosentan for improvement in exercise capacity. For other outcomes and safety, riociguat was non-inferior to bosentan. The efficacy claim was not entirely supported by the evidence, given that change in WHO functional class was not definitively in favour of riociguat.
* Riociguat vs sildenafil: the re-submission did not make a clinical claim regarding the comparative effectiveness and safety of riociguat and sildenafil. The re‑submission reiterated the riociguat versus placebo treatment effect from CHEST-1, as well as the lack of evidence to support the use of sildenafil for the treatment of CTEPH. On the basis of insufficient evidence, no clinical conclusion can be made for the comparative effectiveness or safety of riociguat and sildenafil.
  1. The economic model was solely based on the comparison of riociguat and placebo. Results from the indirect comparisons were not applied in the economic evaluation.
  2. The PBAC considered that the claim of superior comparative effectiveness was reasonable in terms of improvements in 6MWD and WHO functional class. 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). However, the PBAC considered that the claim of a relationship between changes in WHO functional class and survival was not adequately supported and could not be quantified.
  3. The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

## Economic analysis

* 1. The re-submission presented a modelled cost utility analysis.

Table 5: 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 | Markov state transition model: 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 WHO functional class (exponential extrapolation) and age dependent (ABS life tables). It was assumed that for placebo improvements or worsening in WHO FC were only able to occur in the first cycle. Subsequent to the first cycle, placebo patients were only permitted to have a worsening of WHO FC. | | | |
| 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^ | Condliffe 2008 (non-surgical CTEPH cohort): HR = 3.41 |
| Probability of treatment discontinuation: CHEST-1 | | | |

^ Following the first cycle, the re-submission assumes no functional class improvements for placebo treated patients.

Abbreviations: ABS = Australian Bureau of Statistics; FC = functional class; LYG = life years gained; QALY = quality adjusted life years. Source: compiled during the evaluation.

Table 6: Key drivers of the model

| **Description** | **Method/Value** | **Impact** |
| --- | --- | --- |
| Placebo survival extrapolation | Constant hazards approach derived from Condliffe 2008 (non-surgical CTEPH cohort): HR = 3.41 | High, favours riociguat |
| WHO FCTP | Log normal extrapolation of data from CHEST-1 and CHEST-2 to 15 years | High, favours riociguat |
| Time horizon | 15 years | Moderate, favours riociguat |

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

* 1. From a conceptual standpoint, the economic model was structured on the basis of the relationship between WHO functional class and survival (for which the presented rationale was limited). As the relationship between these factors could not be definitively quantified, this led to an underlying disconnect in the economic model. The PSCR argued that the analysis is consistent with the published literature and had a high degree of internal validity because ‘survival was estimated by fitting a parametric function to the observed survival of patients in each WHO functional class’. The ESC considered that it was not appropriate to apply survival estimates based on improvements in WHO functional class.
  2. The ESC noted that the reliability of the economic model was compromised by the following additional 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 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 WHO functional class. In addition, an observational dataset was used to calculate 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 pre-PBAC response argued that the persistence of treatment related benefits for riociguat over the 15 year model time frame was appropriate and in line with the requested restriction which includes strict continuation rules based on those currently implemented for PAH.
* Placebo survival estimates were based on a non-surgical cohort from Condliffe 2008. Given the relatively lower probability of mortality in surgically treated patients, compared with the non-surgical cohort (see Figure 1), the exclusion of persistent CTEPH patients may have resulted in the underestimation of placebo survival. Incremental survival in the model provided by the submission was therefore possibly overestimated.
* The PSCR acknowledged concerns regarding the use of the non-surgical cohort from Condliffe 2008. The PSCR presented an additional analysis of survival from the surgically treated cohort which assumed that results from the surgical cohort are representative of the survival of patients with persistent CTEPH following PEA (see paragraph 6.28).
* Applicability of the modelled treatment effect in the PBS population: reasons for inoperability were not reported in CHEST-1. Given the subjectivity associated with the assessment of operability in CTEPH and the considerable differences in survival across non-operated subgroups (Hurdman 2012), there was concern regarding the certainty of the treatment effect estimated in the economic model.
* The PSCR argued that similarity in the proportion of inoperable and operable CTEPH in the CHEST-1 trial and the Australian population suggested the applicability of the operability assessment used in the trial setting. Furthermore, the PSCR claimed that it is unlikely that the surgical expertise of Australian surgeons would be significantly worse as training often occurs in European/US hospital centres. Acknowledging the complexity involved in the assessment of operability in CTEPH, the PSCR proposed that adjudication by a local expert PEA centre be considered as a potential criterion within the restriction.
* Inadequate patient numbers (n≤10) to reliably determine transition probabilities and utilities associated with WHO functional class IV.

*Figure 1: Kaplan Meier estimates from Condliffe 2008*

| ***A: Surgically treated and non-surgical patients*** | ***B: Post PEA patients*** |
| --- | --- |
| This diagram presents the kaplan meier estimates of surgically treated versus non-surgical patients | This diagram presents the kaplan meier estimates of patients post PEA who have persistent pulmonary hypertension versus those without persistent pulmonary hypertension. |

*Abbreviations: PEA = pulmonary endarterectomy. Source: Figure 1 and 5, Condliffe 2008*

* 1. A minor error in the economic model was identified during the evaluation. The first cycle formula used to calculate the placebo transition probability for functional class II to III incorrectly selected the riociguat intercept and scale instead of the placebo variables. Results for the economic evaluation, presented in the table below, incorporate a correction for this error.

Table 7: Results of the stepped economic evaluation

|  |  |  |  |
| --- | --- | --- | --- |
| **Step and component** | **Riociguat** | **Placebo** | **Increment** |
| **Step 1: trial based economic evaluation (16 weeks)** | | | |
| Costs | $'''''''''''''''''''' | $'''''''''''''' | $'''''''''''' |
| Improvement of ≥1 WHO FC | Risk difference = 0.18 | | NNT = 5.56 |
| **Incremental cost/improvement of ≥1 WHO functional class** | | | $''''''''''''''' |
| **Step 2: modelled economic evaluation: extrapolation to 15 years** | | | |
| Costs | $'''''''''''''''''''''' | $'''''''''''''' | $''''''''''''''' |
| LYG | *5.53* | *4.19* | *1.34* |
| **Incremental cost/LYG** | | | *$'''''''''''''''* |
| **Step 3: modelled economic evaluation: all resource use** | | | |
| Costs | *$'''''''''''''''''''''''* | *$''''''''''''''''''''''''''* | *$''''''''''''''''* |
| LYG | *5.53* | *4.19* | *1.34* |
| **Incremental cost/LYG** | | | *$'''''''''''''''''* |
| **Step 4: modelled economic evaluation: inclusion of utilities** | | | |
| Costs | *$'''''''''''''''''''''''* | *$'''''''''''''''''''''''''* | *$'''''''''''''''* |
| QALY | *3.65* | *2.53* | *1.12* |
| **Incremental cost/QALY** | | | ***$''''''''''''*** |

Note: Figures in *italics* were updated during the evaluation to account for a minor calculation error associated with the calculation of placebo transition probabilities for WHO functional class II to III. Abbreviations: FC = functional class; NNT = number needed to treat. Source: Table D.5-1, Table D.5-2, Table D.5-3 and Table D.5-4, pp 212-214 of the re‑submission.

* 1. While a significant treatment effect was predicted by the economic model, it is likely 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; and
  + the derivation of placebo survival from a non-surgical cohort (Condliffe 2008); see paragraph 6.24 above.
  1. During the evaluation, alternative time points for the duration of riociguat treatment benefits were tested in sensitivity analyses. While median duration of treatment from the CHEST-2 March 2014 cut-off was not reported in the re‑submission, the application of placebo transition probabilities for WHO functional class and mortality from day 599 (median follow-up from CHEST-1 and CHEST-2, June 2012 cut-off) and day 1815 (maximum duration of follow-up from CHEST-2) resulted in ICERs of $105,000 to $200,000 and $75,000 to $105,000, respectively. While the ESC did not consider it was appropriate to apply survival estimates based on improvements in WHO functional class from baseline, this was of moderate consequence to the estimated ICER. When survival estimates based on the overall population instead of WHO functional class were applied to the economic model, the ICER increased by approximately $''''''''''''''' to $45,000 to $75,000 per QALY.
  2. The PCSR presented a revised economic model that incorporated the following changes:
  + A disutility value for dizziness associated with paroxysmal/persistent atrial fibrillation (0.01) was sourced from a conference poster by Doyle et al (2009).
* While the PSCR claimed that the disutility values were calculated using the EQ‑5D, a review of the conference poster indicated that the EQ-5D was only used in the construction of the atrial fibrillation health states presented to participants (n=127, UK general public), with utilities being elicited from a time trade off and ranking task.
  + Revised transition probabilities for death for the placebo group (using surgical and non‑surgical) (see paragraph 6.24).
* The ESC noted that Condliffe 2008 included survival data for patients with persistent CTEPH following surgery which would have been a more appropriate data source (albeit with a small number of patients) to estimate placebo extrapolations of survival for persistent CTEPH patients than the survival data for all surgical CTEPH patients.
* In this regard, the ESC noted that it may have been more appropriate to consider inoperable and persistent CTEPH patients in separate economic models.
  + The cost of placebo treatment was adjusted assuming that the costs of bosentan would apply to 30% of placebo patients ($'''''''''''''''). The PSCR considered this to be a likely underestimate given the reported use of disease modifying therapies in Condliffe 2008. The ESC noted that the costs associated with bosentan were applied as an offset to the riociguat price applied in the economic model, resulting in a reduced cost per day for riociguat ($''''''''''''' vs $'''''''''''''). The ESC considered that this approach likely led to inappropriately low incremental costs due to the following factors:
* There was no consideration for differences in treatment duration for riociguat and bosentan treated patients. Due to the increased survival associated withriociguat treated patients, a more appropriate approach would have been to attribute an increase in drug costs to the placebo arm of the model with an accompanying adjustment to the discontinuation and compliance rates.
* The current settings of the economic model utilise a discontinuation rate of 8.0% for riociguat and 5.7% for placebo. It is unlikely that placebo discontinuation (i.e. bosentan treatment) would be reduced compared with riociguat, considering the re-submission’s claim of superiority for riociguat.
* The pre-PBAC response acknowledged the ESC advice that the additional cost per cycle should have been applied to the placebo group and that the discontinuation rates of placebo and riociguat should be set equal. The response stated that this approach only resulted in a moderate increase in the ICER due to the small incremental life years gained with riociguat compared with placebo.
  1. Results from the revised economic model and accompanying sensitivity analyses are presented in the table below. The estimated ICER is based on a 74%:26% weighting between inoperable CTEPH and persistent CTEPH following PEA. The revised PSCR estimates could not be independently verified. While instructions were provided for the application of the revised placebo survival estimates, it was unclear how disutility for dizziness was incorporated into the revised economic model. The PSCR claimed that applying disutility for dizziness resulted in a change to the ICER of around $'''''''''''''.

Table 8: Revised base case of the economic evaluation and sensitivity analyses (incremental cost per QALY)

|  |  |  |
| --- | --- | --- |
| **Scenario** | **Commentary** | **PSCR** |
| Base case | $''''''''''''''' | $''''''''''''''''' |
| **Sensitivity analyses** | | |
| Day 599 – adjusted mortality | $'''''''''''''''''''' | $''''''''''''''' |
| Day 599 – adjusted mortality and functional class probabilities | $'''''''''''''''''''' | $''''''''''''''' |
| Day 1815 – adjusted mortality | $'''''''''''''''' | $'''''''''''''''' |
| Day 1815 – adjusted mortality and functional class probabilities | $'''''''''''''''' | $'''''''''''''''''' |
| Placebo mortality hazard ratio – 2.5 | $'''''''''''''''''' | $'''''''''''''''''' |
| Placebo mortality hazard ratio – 1.5 | $'''''''''''''''''' | $'''''''''''''''''' |
| Non-functional class dependent survival extrapolation | $''''''''''''''''\* | $''''''''''''''''' |
| No functional class improvement from class IV | $''''''''''''''''' | $''''''''''''''''' |
| Application of EQ-5D utilities from inoperable CTEPH cohort | $''''''''''''''' | $'''''''''''''''' |

\* While the PSCR claimed that a correction was made to the sensitivity analysis for non-functional class dependent survival extrapolation, this ICER was unchanged from the sensitivity analysis in the commentary (Table D.6.1, 05.COM.45).

Source: Table 1, p3 of the PSCR

* 1. Although the revisions to the economic model are expected to decrease incremental life years, QALYs and costs, the inclusion of bosentan cost offsets was the likely dominant factor in the reduced base case ICER ($45,000 to $75,000 per QALY). The ESC noted that survival estimates were only adjusted for the placebo group in the PSCR analysis. Separate survival analyses for riociguat treated patients with inoperable CTEPH and persistent CTEPH were not incorporated into the revised economic model. In addition, there was no consideration for any potential differences in WHO functional class transition probabilities across the inoperable and persistent CTEPH cohorts.
  2. Overall, the ESC questioned whether the revised ICER presented in the PSCR is of sufficient reliability and whether it may have been more appropriate to consider inoperable and persistent CTEPH patients in separate economic models. The pre‑PBAC response argued that further splitting the analyses by operability status would only increase uncertainty given the small numbers of functional class transitions by baseline functional class.
  3. The pre-PBAC response offered a ''''''''% price reduction (resulting in a new effective DPMQ of $''''''''''' for an 84 tablet pack), which it stated was to give the PBAC further certainty of the cost-effectiveness of riociguat within the proposed restriction. In this regard, the response provided a new sensitivity analysis which assumed there would be no survival benefit associated with riociguat for the surgical cohort (and including the price reduction). This scenario resulted in an ICER of around $45,000 to $75,000 for surgical patients, $15,000 to $45,000 for non-surgical patients and $45,000 to $75,000 overall.

## Drug cost/patient/year: $'''''''''''''

* 1. 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 $''''''''''''''''''''' per continuing prescription for all riociguat strengths, the drug cost/patient/year was estimated to be $''''''''''''''''.

## Estimated PBS usage & financial implications

* 1. The re-submission was not considered by DUSC. The re‑submission updated the financial estimates for riociguat, applying revisions included in the November 2014 pre-PBAC response which the PBAC considered to be in line with the DUSC advice (November 2014 riociguat PSD, paragraph 6.24). The submission included additional cost‑offsets associated with an assumed reduction in bosentan use.

Table 9: Estimated use and financial implications

|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** |
| --- | --- | --- | --- | --- | --- |
| **Estimated extent of use** | | | | | |
| Patients treated with riociguat | '''''''''' | ''''''''' | '''''''''' | '''''''''' | '''''''''' |
| November 2014 submission | ''''' | '''''''''' | '''''''' | ''''''''' | '''''''''' |
| November 2014 pre-PBAC response | '''''''''' | ''''''''' | '''''''''' | ''''''''' | ''''''''' |
| **Estimated net cost to PBS/RPBS** | | | | | |
| Net cost to PBS/RPBS | $''''''''''''''''''''''''' | $'''''''''''''''''''''''''' | $''''''''''''''''''''''' | $''''''''''''''''''''' | $''''''''''''''''''''''' |
| November 2014 submission | $''''''''''''''''''''''' | $'''''''''''''''''''''' | $''''''''''''''''''''''''' | $''''''''''''''''''''''''' | $''''''''''''''''''''''''' |
| November 2014 pre-PBAC response | $'''''''''''''''''''''''''' | $''''''''''''''''''''''' | $''''''''''''''''''''''' | $''''''''''''''''''''''''' | $''''''''''''''''''''''' |
| Estimated changes in the use and cost of bosentan associated with the listing of riociguat | | | | | |
| Reduction in bosentan patients | ''''''' | ''''' | ''''''' | '''''''' | ''''''''' |
| Net savings in bosentan cost to PBS/RPBS | $''''''''''''''''''''''''' | $''''''''''''''''''''''' | $''''''''''''''''''''''' | $'''''''''''''''''''''' | $''''''''''''''''''''''' |
| Net savings in bosentan LFT costs to MBS | $'''''''''''''' | $''''''''''''''' | $'''''''''''''''' | $'''''''''''''''' | $'''''''''''''''' |
| **Total net cost to government** | **$''''''''''''''''''** | **$'''''''''''''''''''''** | **$''''''''''''''''''** | **$'''''''''''''''''''''** | **$'''''''''''''''''''''** |
| November 2014 submission | $''''''''''''''''''''' | $''''''''''''''''''''''' | $''''''''''''''''''''''' | $''''''''''''''''''''''''''' | $''''''''''''''''''''''''''' |
| November 2014 pre-PBAC response | $''''''''''''''''''''''' | $'''''''''''''''''''''''' | $''''''''''''''''''''''' | $''''''''''''''''''''''' | $'''''''''''''''''''''' |

Source: Table E.2-5, p231; Table E.3-2, p232; Table E.3-3, p232; Table E.4-1, p233 and Table E.5-3, p234 of the re-submission

* 1. It is unlikely that the extent of bosentan 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. While misclassification of CTEPH occurs in clinical practice, increased disease state awareness would only be expected to gradually influence the switching rate from PBS subsidised bosentan to riociguat, as opposed to the constant rate (30%) that was applied in the financial estimates. The PSCR considered that this was a reasonable comment and revised the extent of substitution from bosentan treatment, with a decrease from 30% in Year 1 to 0% in Year 5. The revised financial estimates for Year 1 were unchanged while the net cost to the government increased to $8.6 million (from $5.6 million) in Year 5.
  2. 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 cost off-sets.
  3. The redacted table above shows that in 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.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

1. PBAC Outcome
   1. 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.
   2. The PBAC recalled it rejected a submission requesting PBS-listing of riociguat for the treatment of inoperable or persistent CTEPH following PEA in November 2014, as the cost-effectiveness of riociguat for this indication had not been established against the appropriate comparator.
   3. 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.
   4. The PBAC noted that as per the November 2014 submission, 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 35-50 metres. The PBAC further noted the statistically significant improvement of at least one WHO functional class associated with riociguat, compared with placebo.
   5. 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. The PBAC considered that the claim of a relationship between changes in WHO functional class and survival was not adequately supported and could not be quantified.
   6. 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 was inferior with regards to comparative safety, compared with 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. The PBAC noted that the model was structured on the basis of the relationship between WHO functional class and survival, whereas the trial was based on the 6MWD test. The PBAC agreed with ESC that this produced an underlying disconnect between the model and the clinical data, and considered that while there was some evidence to support the relationship between WHO functional class and survival gain, there was still considerable uncertainty regarding the survival gain associated with improvements in this measure.
   8. The PBAC considered that the economic analysis favoured riociguat, and agreed with the ESC that there was uncertainty around a number of model parameters. In particular, the PBAC noted:

* There were inadequate patient numbers (n≤10) to reliably determine transition probabilities and utilities associated with WHO functional class IV.
* The magnitude of the change in the ICER (compared with the base case) as a result of assuming that the costs of bosentan apply for 30% of placebo patients in the revised model presented in the PSCR. The PBAC considered that as this was an important driver of the model, this major assumption should have been better supported.
* The assumption of ongoing treatment benefits for riociguat over 15 years may not have been reasonable.
* The use of placebo survival estimates based on a non-surgical cohort from Condliffe 2008 which may have overestimated incremental difference in survival. The PBAC noted that there were several exclusions from the non-surgical cohort in Condliffe 2008 which suggested that survival in this group may not be representative of the relevant population.
  1. The PBAC noted that the financial implications assumed significant savings from reduction in the use of bosentan which may not be realised.
  2. The PBAC considered that a major re-submission would be required to seek listing of riociguat for inoperable CTEPH and persistent CTEPH following surgery. The re‑submission should present a revised model that addresses the issues outlined in paragraphs 7.7-7.8.
  3. The PBAC noted that this submission is eligible for an independent review.

**Outcome:**

Rejected

1. Context for Decision
   1. 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.
2. Sponsor’s Comment

Bayer is disappointed by the PBAC decision, however will continue to work with the Department, PBAC and the medical community to progress the reimbursement of riociguat.

As noted in the outcome, transitions in WHO functional class were the basis of the health states modelled, this structure is consistent with the published health economic literature for cost-effectiveness analyses in pulmonary hypertension. Inoperable or persistent CTEPH is a rare orphan designated disease, which means there will always be intrinsic analytical challenges with the translation of RCT evidence to health economic modelling.

Bayer will continue to work towards addressing the PBACs concerns and strive for solutions to bring subsidised therapy to Australian CTEPH patients.

1. Although the re-submission claimed a significant difference for headache, this was not reflected in the statistical analyses (RR=1.96, 95% CI 0.89, 4.33; RD%=7.7, 95% CI: -0.17, 15.4). [↑](#footnote-ref-1)