

**7.07 SELEXIPAG,  
Tablets, 200, 400, 600, 800, 1000, 1200, 1400 and  
1600 micrograms,  
Upravi<sup>®</sup>, Actelion Pharmaceuticals Australia.**

**1 Purpose of Application**

1.1 The resubmission requested a Section 100, Authority Required listing for selexipag for treatment of pulmonary arterial hypertension (PAH).

**2 Requested listing**

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty*	Proprietary Name and Manufacturer
SELEXIPAG				
Tablet 200 microgram, 140	1	2	\$ [REDACTED] (private)	Upravi <sup>®</sup> Actelion
Tablet 800 microgram, 60	1	1	\$ [REDACTED] (public)	Pharmaceuticals
*Special pricing arrangement proposed: effective price \$ [REDACTED] (private), \$ [REDACTED] (public)				

2.1 The proposed effective price in the resubmission was \$ [REDACTED] lower than the previous submission, due to an increase in the proposed rebate (\$ [REDACTED]/prescription compared to \$ [REDACTED] in the previous submission).

2.2 The requested listings were largely consistent with the Secretariat's suggested listings from the March 2016 submission, with the main exception being that the resubmission specifically requested use as triple therapy only, while the previous submission included both dual and triple therapy.

2.3 The proposed restriction did not discuss the eligibility of patients who are intolerant or contraindicated to either ERAs or PDE-5 inhibitors, although the resubmission stated that dual therapy with selexipag is intended in these circumstances. As it is currently written, the proposed listing would not permit dual therapy with selexipag and an ERA or a PDE-5 inhibitor. The Pre-Sub-Committee Response (PSCR) confirmed that the submission's intention was to permit dual therapy for patients who are intolerant or contraindicated to either ERAs or PDE-5 inhibitors.

2.4 The requested PBS listing was more restrictive than the approved TGA indication, which permits use of selexipag as any of mono-, dual or triple therapy.

2.5 The listing of selexipag was sought on the basis of cost-effectiveness compared with placebo. This is appropriate.

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

### **3 Background**

- 3.1 Selexipag was TGA registered on 24 March 2016 for the treatment of patients with WHO functional class II, III or IV symptoms with:
- idiopathic pulmonary arterial hypertension;
  - heritable pulmonary arterial hypertension;
  - pulmonary arterial hypertension associated with connective tissue disease;
  - pulmonary arterial hypertension associated with congenital heart disease with repaired shunts; and
  - pulmonary arterial hypertension associated with drugs and toxins.
- 3.2 This was the second submission requesting PBS listing of selexipag for treatment of PAH. The PBAC previously considered a major submission for selexipag for the treatment of PAH in combination with an ERA and/or a PDE-5 inhibitor at the March 2016 PBAC meeting. Selexipag was not recommended for listing on the basis that the magnitude of clinical benefit was unclear, and the estimate of cost-effectiveness was difficult to interpret (paragraph 7.1, 5.11 selexipag public summary document (PSD), March 2016 PBAC meeting).
- 3.3 As of November 2016, PBS subsidy was available for the following medicines for WHO FC III and/or IV PAH: bosentan, macitentan, and ambrisentan (ERAs), sildenafil and tadalafil (PDE-5 inhibitors), epoprostenol and iloprost (prostanoids). Under current restrictions for PAH drugs, patients are only eligible for PBS subsidised treatment with one PAH agent at any time.

### **4 Clinical place for the proposed therapy**

- 4.1 The resubmission proposed that patients with inadequate response to first-line monotherapy with either an ERA or PDE-5 inhibitor would progress to dual therapy with an ERA and a PDE-5 inhibitor. It was proposed that selexipag be used in combination with both an ERA and a PDE-5 inhibitor. The proposed clinical management algorithm was consistent with recent international clinical practice guidelines.
- 4.2 In practice, a proportion of patients will be intolerant or contra-indicated to either an ERA or PDE-5 inhibitor, and, as clarified in the PSCR, may use selexipag as in combination with only one other drug.

### **5 Comparator**

- 5.1 The resubmission nominated placebo as the main comparator. The PBAC agreed that placebo (as add-on to combination therapy) was the appropriate comparator for the previous submission (paragraph 7.3, 5.11 selexipag PSD, March 2016 PBAC meeting).

### **6 Consideration of the evidence**

#### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The sponsor reiterated the company's proposal to rebate 100% of the cost of sildenafil when used as an add-on to Actelion-sponsored ERA products. The clinician explained that ERAs and PDE-5 inhibitors are the preferred first- and second-line treatments for PAH because, compared to selexipag, they have earlier onset of action, do not require dose titration, have fewer adverse events and can generally be taken once daily. The clinician emphasised that selexipag is a practical third-line treatment, particularly for patients who are not ready for treatment with intravenous epoprostenol, which is the standard treatment for high-risk PAH. However, administration of epoprostenol is complex, burdensome and can cause adverse reactions at the administration site.

**Consumer comments**

- 6.2 The PBAC noted and welcomed the input from individuals (33), health care professionals (9) and organisations (4) via the Consumer Comments facility on the PBS website. The comments described some benefits of treatment with selexipag including the convenience of oral rather than intravenous administration, and that it provides an additional treatment option for patients. Some input also supported the use of combination therapy for PAH on the PBS in general.

**Clinical trials**

- 6.3 The resubmission was based on one head-to-head randomised trial (GRIPHON) comparing selexipag, with or without background PAH-specific therapy (an ERA and/or PDE-5 inhibitor), to placebo with or without background PAH specific therapy (n=1,156). This was the same trial considered in the previous submission. The GRIPHON study included monotherapy and dual therapy, as well as triple therapy.
- 6.4 Details of the trial presented in the submission are provided in the table below.

**Table 1: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trial</b>		
GRIPHON	GRIPHON Clinical study report AC-065A302: Prostacyclin (PGI <sub>2</sub> ) receptor agonist in pulmonary arterial hypertension: A multicenter, double-blind, placebo-controlled Phase 3 study assessing the efficacy and safety of selexipag (ACT-293987) on morbidity and mortality in patients with pulmonary arterial hypertension (PAH) (including data from AC-065A303/GRIPHON OL up to 10 March 2014).  Sitbon O, Channick R, <i>et al.</i> Selexipag for the treatment of pulmonary arterial hypertension.	March 2014 (data cut-off)  <i>New England Journal of Medicine</i> 2015; 373 (26):2522-2533

Source: Table 1, 5.11 selexipag public summary document, March 2016 PBAC meeting

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

**Table 2: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome	Use in economic evaluation
<b>Selexipag ± BGT vs. placebo ± BGT</b>						
GRIPHON	1,156	MC, R, DB 71/64 weeks <sup>a</sup>	Low <sup>b</sup>	WHO FC I-IV Treatment naive or receiving other PAH specific treatment	Time to first morbidity or mortality (MM) event <sup>c</sup>	First MM event rate

BGT = background therapy; DB=double blind; MC=multi-centre; MM = morbidity or mortality; PAH = pulmonary arterial hypertension; R=randomised; WHO FC = World Health Organization Functional class.

<sup>a</sup> Median duration of study treatment in the selexipag/placebo treatment arms.

<sup>b</sup> While different rates of censoring between the randomised groups biased the results of the primary outcome, favouring selexipag, sensitivity analyses indicated that the conclusion of superiority for selexipag ± BGT over placebo ± BGT was robust.

<sup>c</sup> Composite outcome including (see below)

Source: Table 2, 5.11 selexipag public summary document, March 2016 PBAC meeting

6.6 The primary outcome in the GRIPHON trial was time to first Critical Event Committee (CEC)-confirmed morbidity or mortality (MM) event up to end-of-treatment (EOT) plus 7 days. This composite outcome included the following component endpoints:

- All-cause mortality;
- Hospitalisation for worsening PAH;
- Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy;
- Initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening PAH; and
- Disease progression, confirmed by decrease in 6 minute walk distance (6MWD) from baseline of at least 15%, and either worsening of WHO FC or need for additional PAH specific therapy (depending on WHO FC at baseline).

The PBAC previously considered the time to first MM event a more patient relevant outcome than the 6MWD (5.11 macitentan PSD, March 2014 PBAC meeting). However, the PBAC stated that the use of a composite outcome where, for example, death has the same clinical relevance as hospitalisation made the results difficult to interpret. The PBAC stated that a translation of the time to first MM event to life-years gained or quality-adjusted life-years (QALYs) would be more informative (5.11 selexipag PSD, March 2016 PBAC meeting).

6.7 The outcomes of the key trial were subject to the following limitations:

- Patients who experienced a non-fatal primary endpoint event may have ceased study treatment. Consequently, time-to-event data may have been compromised by censoring for subsequent components of the composite endpoint; and
- Patients who discontinued treatment early (before study closure) without a primary outcome event, including for reasons such as discontinuation due to adverse events, were censored at this time point, rather than being followed to the end of the study. In the intention-to-treat (ITT) population, 22.6% of patients in the selexipag ± background therapy (BGT) treatment group and 15.1% in the placebo ± BGT group were censored early. This differential censoring biased the treatment effect estimates in favour of selexipag. The ESC acknowledged the comments in the PSCR around aspects of trial design

that might have biased the results of GRIPHON against selexipag, and considered that these issues added to the overall uncertainty around the trial results.

- 6.8 The resubmission presented an alternative composite outcome defined by the Committee for Medicinal Products for Human Use (CHMP). The CHMP-defined MM components were: death, hospitalisations for PAH worsening, increase in WHO FC, signs/symptoms of right-sided heart failure (RHF) and  $\geq 15\%$  decrease in 6MWD from baseline. The CHMP composite outcome differs from the primary outcome and is subject to the same limitations of the primary outcome discussed above. The ESC noted that the main differences were that initiation of chronic oxygen or parenteral prostanoid therapy or the need for lung transplantation or balloon atrial septostomy in the study definition of MM was replaced by signs/symptoms of RHF in the CHMP-defined MM. The estimates of the CHMP composite outcome and its individual components had a risk of bias especially in the retrospective diagnosis of RHF.
- 6.9 The resubmission also presented time to first event for individual morbidity components of the CHMP composite outcome. As patients were only followed to EOT + 7 days, events that occurred more than 7 days after treatment discontinuation were not captured.
- 6.10 Overall survival at the end of study was reported. This was presented as a secondary outcome in the previous submission.

### ***Comparative effectiveness***

- 6.11 Table 3 summarises the results for ITT analysis of time to first CHMP-defined MM event up to EOT + 7 days. Figure 1 presents the Kaplan-Meier curve of time to first CHMP-defined event for the full analysis set.

**Table 3: First CHMP-defined MM event and individual CHMP component events up to EOT plus 7 days in the GRIPHON trial (ITT)**

	Selexipag ± BGT N=574	Placebo ± BGT N=582	
Median duration of follow-up, weeks (IQR) <sup>a</sup>	70.7 (32.0, 117.1)	63.7 (28.6, 107.1)	
<b>First CHMP-defined MM event</b>	<b>n (%)</b>	<b>n (%)</b>	<b>Time to event HR [99% CI], 1-sided p-value</b>
Patients with CHMP-defined MM event to EOT+7 days	268 (46.7%)	343 (58.9%)	0.73 [0.60, 0.91], <0.0001
<b>Individual CHMP component events<sup>b</sup></b>	<b>n (%)</b>	<b>n (%)</b>	<b>Time to event HR [95% CI], 1-sided p-value</b>
Death	46 (8.0%)	37 (6.4%)	NR
Hospitalisation for PAH worsening	86 (15.0%)	124 (21.3%)	0.65 [0.50, 0.86], p<0.0001
Increase in WHO FC from baseline	122 (21.3%)	178 (30.6%)	0.65 [0.52, 0.82], p<0.0001
Signs/symptoms of right-sided heart failure	160 (27.9%)	247 (42.4%)	0.60 [0.49, 0.74], p<0.0001
≥15% decrease in 6MWD from baseline	198 (34.5%)	284 (48.8%)	0.66 [0.55, 0.80], p<0.0001

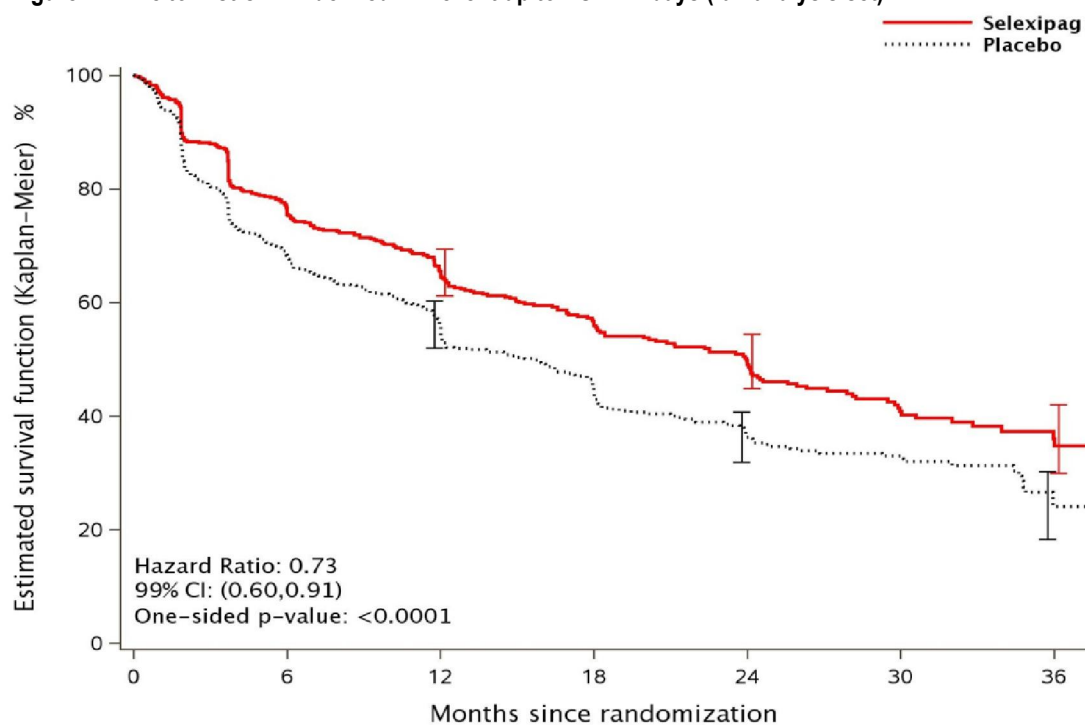
6MWD = 6-minute walk distance; BGT = background therapy; CHMP = Committee for Medicinal Products for Human Use; CI = confidence interval; EOT = end-of-treatment; FC = functional class; IQR = interquartile range; ITT = intention-to-treat; MM = morbidity or mortality; PAH = pulmonary arterial hypertension; WHO = World Health Organization.

<sup>a</sup> Safety analysis set

<sup>b</sup> In these analyses, all events that occurred prior to EOT + 7 days were counted, *i.e.* not only the first event contributing to the composite endpoint. Time to individual CHMP component events is only available for patients who remained on treatment. Patients who stopped trial treatment for any reason (an MM event, adverse event) were censored.

Source: Table 15, p49, Figure 12, p48, Table 16, p49 and Figures 13-16, pp50-53 of the resubmission

**Figure 1: Time to first CHMP-defined MM event up to EOT + 7 days (full analysis set)**



CHMP = Committee for Medicinal Products for Human Use; EOT = end of treatment; MM = morbidity or mortality.

Note: vertical bars represent 95% confidence intervals.

Source: Figure 12, p48 of the resubmission

- 6.12 An estimate of the effect on time to individual CHMP-defined MM events (hospitalisation, signs or symptoms of right-sided heart failure, worsening of functional class or  $\geq 15\%$  drop in 6MWD) was presented for subgroups based on WHO FC and PAH therapy at baseline (pp 44-47 of the resubmission). These results were difficult to interpret because treatment allocation was not stratified by subgroups. Also, the resubmission did not present the results for patients who are both WHO FC III/IV and receiving dual therapy at baseline to match the proposed restriction. Additionally, the issue of subsequent events occurring after EOT definition (and hence not being captured) made this result even more uncertain.
- 6.13 All-cause mortality from randomisation to study closure was reported to be 17.4% and 18.0% of patients in the selexipag and placebo groups, respectively. This differs from the estimate of all-cause mortality up to EOT + 7 days which was confounded by informative censoring. The comparison of all-cause mortality at study closure is potentially confounded in favour of placebo as 27% of patients from the placebo arm switched to selexipag treatment after an MM event.

### ***Comparative harms***

- 6.14 No additional safety data were provided with the resubmission. The most frequently reported adverse events were those associated with prostacyclins, and occurred more commonly in the selexipag arm compared with placebo. As selexipag is titrated to the maximum tolerable dose, the number of adverse events during the titration phase is greater than in the maintenance phase during which patients are dosed at one increment lower than the dose which resulted in an adverse event.

### ***Benefits/harms***

- 6.15 A summary of the comparative benefits and harms for selexipag  $\pm$  BGT and placebo  $\pm$  BGT in the GRIPHON trial are presented below. Event rates, risk ratios and risk differences have been presented as the resubmission did not report median time to first CHMP-defined MM event or time to the individual events.

Table 4: Summary of comparative benefits and harms for selexipag ± BGT and placebo ± BGT in the GRIPHON trial

GRIPHON: whole of trial population	Selexipag ± BGT	PBO ± BGT	RR (95% CI) <sup>a</sup>	Event rate/100 patients <sup>b</sup>		RD (95% CI) <sup>a</sup>
				Selexipag ± BGT	PBO ± BGT	
<b>Benefits</b>						
<b>CHMP-defined MM event</b>						
Patients with event	268/574	343/582	0.79 (0.71, 0.88)	46.7	58.9	-0.12 (-0.18, -0.07)
<b>Individual CHMP-defined MM events<sup>c</sup></b>						
Hospitalisation for PAH worsening	86/574	124/582	0.7 (0.55, 0.9)	15	21.3	-0.06 (-0.11, -0.02)
Increase in WHO FC from baseline	122/574	178/582	0.69 (0.57, 0.85)	21.3	30.6	-0.09 (-0.14, -0.04)
Signs/symptoms of right-sided heart failure	160/574	247/582	0.66 (0.56, 0.77)	27.9	42.4	-0.15 (-0.2, -0.09)
≥15% decrease in 6MWD from baseline	198/574	284/582	0.71 (0.61, 0.81)	34.5	48.8	-0.14 (-0.2, -0.09)
<b>Harms</b>						
	Selexipag ± BGT	Placebo ± BGT	RR (95% CI)	Event rate/100 patients <sup>b</sup>		RD (95% CI)
	Selexipag ± BGT	Placebo ± BGT	RR (95% CI)	Selexipag ± BGT	Placebo ± BGT	RD (95% CI)
<b>Death up to EOT + 7 days (not due to PAH)</b>						
GRIPHON	13/575	10/577	1.30 (0.58, 2.95)	2.3	1.7	0.5% (-1.1%, 2.1%)
<b>Discontinuation due to AE without a primary outcome event<sup>d</sup></b>						
GRIPHON	82/575	41/577	2.00 (1.40, 2.87)	14.3	7.1	7.2% (3.6%, 10.7%)
<b>Prostacyclin-associated AEs leading to discontinuation</b>						
GRIPHON	59/575	11/577	5.38 (2.86, 10.14)	10.3	1.9	8.4% (5.6%, 11.1%)

6MWD = 6-minute walk distance; AE = adverse event; BGT = background therapy; CI = confidence interval; FC = functional class; MM = morbidity or mortality; NA = not available; PAH = pulmonary arterial hypertension; RD = risk difference; RR = risk ratio

<sup>a</sup> Relative risks, risk differences and confidence intervals generated during the evaluation.

<sup>b</sup> Median duration of exposure: 70.7 weeks in the selexipag arm and 63.7 weeks in the placebo arm

<sup>c</sup> All events that occurred prior to 7 days after the end of treatment were counted, *i.e.* not only the first event contributing to the composite endpoint.

<sup>d</sup> This analysis included patients who discontinued study drug prior to Study closure who did not have a CEC-confirmed MM event with an onset date prior to or on the date of study drug discontinuation *i.e.* AE not classified as PAH progression.

Source: Compiled during the evaluation

6.16 On the basis of the direct evidence presented by the submission, for every 100 patients treated for 64-71 weeks with selexipag ± BGT in comparison to placebo ± BGT:

- Approximately 12 fewer patients would have experienced a CHMP-defined MM event (any of: death, hospitalisations for PAH worsening, increase in WHO FC, signs/symptoms of right-sided heart failure (RHF) and ≥ 15% decrease in 6MWD from baseline);
- Approximately 7 additional patients would discontinue treatment due to an adverse event not classified as PAH progression;
- Approximately 8 additional patients would discontinue treatment due to a prostacyclin-associated adverse event.

**Clinical claim**

- 6.17 The previous submission described selexipag as superior in terms of comparative effectiveness and inferior in terms of comparative safety, when used as add-on therapy for the treatment of patients with WHO FC III or IV PAH. The PBAC accepted that selexipag was inferior in terms of comparative safety (paragraph 6.25, 5.11 selexipag PSD, March 2016 PBAC meeting) and was likely to be superior in terms of comparative effectiveness, but the magnitude and clinical relevance of any benefit remained unclear (paragraph 7.6, 5.11 selexipag PSD, March 2016 PBAC meeting).
- 6.18 The clinical claim was unchanged in the resubmission. To address the concerns of the PBAC regarding the clinical relevance of the effectiveness data, the resubmission presented time to CHMP-defined MM event as well as the individual components of the CHMP-defined composite outcomes. The resubmission claimed that time to the CHMP composite endpoint reflects time to clinical worsening. The results of the CHMP-defined MM endpoints up to EOT + 7 days in the overall trial population supported the superior comparative effectiveness of selexipag versus placebo.
- 6.19 The following concerns with the magnitude of the clinical benefit remained:
- The ITT population did not reflect the proposed PBS reimbursed population in terms of WHO FC or PAH therapy at baseline. The PSCR noted that the submission undertook an investigation to determine whether the factors upon which the subgroup is defined are modifiers of treatment effect or not, and claimed that the results of these analyses indicated that neither WHO-FC nor background therapy were modifiers of treatment effect (in terms of impact on any of the CHMP component endpoints) of selexipag vs placebo. The ESC noted this information, but considered that this issue remained unresolved;
  - Treatment allocation was not stratified by either WHO FC or treatment at baseline, and subgroup analyses should be interpreted with caution;
  - CHMP-defined morbidity outcomes, especially retrospective assessment of RHF, might have a degree of subjectivity and there was potential for un-blinding of investigators;
  - Censoring prior to a CHMP-defined MM event was greater in the selexipag arm, which would favour selexipag;
  - Patients were censored following the first CHMP-defined MM event if they stopped study treatment, making the estimate of time to individual components of the CHMP-defined events less reliable;
  - There was no evidence that selexipag was superior to placebo in terms of overall survival, although this may be affected by switching from placebo to selexipag. The ESC acknowledged that the GRIPHON study was not powered to detect a difference in mortality.
- 6.20 The PBAC remained of the view that selexipag was likely to be superior to placebo in terms of comparative effectiveness, but the magnitude and clinical relevance of any benefit remained unclear.

### **Economic analysis**

- 6.21 The resubmission presented a trial-based cost-effectiveness analysis which gave an incremental cost per reduction in the number of patients with individual CHMP-defined events at 2 years.

### Healthcare costs

- 6.22 The only healthcare cost considered in the economic evaluation was the proposed effective price of selexipag for one month. The cost of selexipag was re-calculated to reflect the average duration of treatment in the trial for the whole of trial population, truncated at 2 years.

### Health outcomes

- 6.23 The resubmission estimated the incremental treatment effect compared to placebo, in terms of the reduction in the number of patients with individual CHMP-defined morbidity events at 2 years.
- 6.24 The numbers of patients with events at 2 years in the placebo arm for each of the component events were reported from the GRIPHON trial for patients with WHO FC III/IV PAH who were receiving treatment with both an ERA and PDE-5 inhibitor at baseline. This post hoc subgroup reflects the proposed restriction. The resubmission estimated the number of patients with each CHMP-defined component event in the selexipag arm for the same subgroup by multiplying the event rate at 2 years in the placebo arm by the hazard ratio for the ITT population. The resubmission justified using the hazard ratios derived from the ITT population on the basis that interaction tests between the WHO FC subgroups and between the baseline therapy subgroups indicated no statistically significant heterogeneity. The approach is incorrect and inappropriate.
- Tests for interaction are generally underpowered to detect meaningful differences in treatment effect between subgroups;
  - The resubmission has not established that there is no treatment effect modification between the target subgroup (WHO FC III/IV and dual therapy at baseline) and its complement;
  - The approach assumes that the hazard ratio is applicable to the 2 year time point. However, the resubmission has not addressed the assumption of proportional hazards for either the ITT analysis or for the relevant subgroups;
  - The multiplication of the event rate in the placebo arm by the hazard ratio is mathematically incorrect; and,
  - As the resubmission had the capacity to generate the event rate at 2 years for the placebo arm in the relevant subgroup using empirical data, it is unclear why this was not done for the selexipag arm. Justification for not providing these data was not provided in the resubmission.

The PSCR (Table 1, p5) provided the test for proportional hazards which demonstrated that, for the full analysis set, there was no treatment by time interaction for the CHMP component endpoints. The ESC considered that the submission's use of a different approach to calculate the event rate in the selexipag arm than was used to calculate the event rate in the placebo arm remained inadequately justified.

Therefore the ESC considered that the results reported were unlikely to be a reliable estimate of the true difference in event rates at 2 years.

**Table 5: Event rate estimates at 2 years in the WHO FC III/IV and baseline dual therapy subgroup**

CHMP endpoint	Placebo + BGT	ITT HR <sup>a</sup>	Selexipag + BGT <sup>b</sup>	Incremental outcome <sup>a</sup>
Hospitalisation for PAH worsening	█%	█	█%	█%
Increase in FC	█%	█	█%	█%
Signs / symptoms of right-sided heart failure	█%	█	█%	█%
≥ 15% decrease in 6MWD	█%	█	█%	█%

6MWD = 6-minute walk distance; BGT = background therapy; CHMP = Committee for Medicinal Products for Human Use; FC = functional class; HR = hazard ratio; ITT = intention-to-treat; PAH = pulmonary arterial hypertension

<sup>a</sup> Selexipag + BGT versus Placebo + BGT

<sup>b</sup> Derived by multiplying the HRs for the ITT population and the respective baseline rate in the placebo arm.

Source: Figures 13-16, pp50-53 and Table 20, p61 of the resubmission

6.25 Notwithstanding the concerns with the approach described above, the estimate of the difference in the event rates at 2 years for each of the CHMP-defined endpoints may be affected by:

- Greater censoring in the selexipag arm prior to any CHMP-defined event;
- Censoring in either arm following the first CHMP-defined event if a decision is made to stop treatment;
- Components of the CHMP-defined endpoints were not collected prospectively and may have required a degree of judgement when adjudicating. The resubmission has not stated that the outcome assessors applying the CHMP endpoint definitions were blinded to treatment allocation;
- The occurrence of adverse events typical of prostacyclin receptor agonists, particularly during the titration phase, is likely to have led to a degree of unblinding of investigators and patients.

The true difference in event rates at 2 years cannot be reliably estimated from the evidence presented or the approach taken in the resubmission.

6.26 Results of the economic evaluation are presented below:

**Table 6: Results of the economic evaluation for selexipag versus placebo as add-on therapy to ERA + PDE-5 inhibitor for patients with WHO FC III or IV PAH**

	Selexipag	Placebo	Increment
Costs <sup>a</sup>	\$ [REDACTED]	\$0	\$ [REDACTED]
Proportion of patients with hospitalisation for PAH worsening at Year 2	[REDACTED]%	[REDACTED]%	[REDACTED]%
<b>Incremental cost / patient with hospitalisation for PAH worsening avoided at Year 2</b>			<b>\$ [REDACTED]</b>
Costs <sup>a</sup>	\$ [REDACTED]	\$0	\$ [REDACTED]
Proportion of patients with increased WHO FC at Year 2	[REDACTED]%	[REDACTED]%	[REDACTED]%
<b>Incremental cost / patient with increased WHO FC avoided at Year 2</b>			<b>\$ [REDACTED]</b>
Costs <sup>a</sup>	\$ [REDACTED]	\$0	\$ [REDACTED]
Proportion of patients with signs/symptoms of right-sided heart failure at Year 2	[REDACTED]%	[REDACTED]%	[REDACTED]%
<b>Incremental cost / patient with signs/symptoms of RS heart failure avoided at Year 2</b>			<b>\$ [REDACTED]</b>
Costs <sup>a</sup>	\$ [REDACTED]	\$0	\$ [REDACTED]
Number patients with ≥15% decrease in 6MWD at Year 2	[REDACTED]%	[REDACTED]%	[REDACTED]%
<b>Incremental cost / patient with ≥15% decrease in 6MWD avoided at Year 2</b>			<b>\$ [REDACTED]</b>

6MWD = 6-minute walk distance; ERA = endothelin receptor antagonist; BGT = background therapy; FC = functional class; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type 5; RS = right-sided; WHO = World Health Organization

<sup>a</sup> Costs were re-calculated during the evaluation based on the proposed effective price, 66% of dispensing occurring in public and an average duration of treatment of 65.7 weeks.

Source: Calculated during the evaluation.

The redacted table shows ICERs in the range of more than \$200,000 per incremental cost/patient with hospitalisation for PAH worsening avoided at Year 2; more than \$200,000 per incremental cost / patient with increased WHO FC avoided at Year 2; \$105,000 - \$200,000 per incremental cost / patient with signs/symptoms of RS heart failure avoided at Year 2; and \$105,000 - \$200,000 per incremental cost / patient with ≥15% decrease in 6MWD avoided at Year 2.

- 6.27 Using a similar approach to the previous submission, to assist in the interpretation of the ICERs, the resubmission has presented the ICERs calculated for the same CHMP-defined endpoints for macitentan, which is an ERA listed on the PBS for PAH.
- 6.28 As CHMP-defined endpoints were not collected prospectively for macitentan in the SERAPHIN trial, the resubmission needed to establish both signs/symptoms of right-sided heart failure and hospitalisations for PAH retrospectively from the study case report forms.
- 6.29 The resubmission presented the price for one month of macitentan as the only cost in the economic evaluation. The costs were re-calculated during the evaluation to reflect the average duration of treatment in the macitentan trial truncated at 2 years.
- 6.30 The resubmission estimated the hazard ratios for the time to CHMP-defined endpoints for the ITT population in the SERAPHIN trial. The ITT population contained patients with WHO FC I/II and the resubmission did not present the hazard ratios for the WHO FC III/IV population. The number of patients with CHMP-defined events at 2 years for macitentan in WHO FC III/IV with no background therapy (the PBS subsidised population) was estimated by multiplying the ITT hazard ratio for macitentan *versus* placebo in SERAPHIN with the event rate in the placebo arm from GRIPHON in patients who were WHO FC III/IV and who were on no background therapy.

**Table 7: Event rate estimates at 2 years in the WHO FC III/IV and no treatment at baseline subgroup**

CHMP endpoint	Placebo <sup>a</sup>	ITT HR <sup>b</sup>	Macitentan <sup>c</sup>	Increment outcome <sup>b</sup>
Hospitalisation for PAH worsening	█%	█	█%	█%
Increase in FC	█%	█	█%	█%
Signs / symptoms of right-sided heart failure	█%	█	█%	█%
≥ 15% decrease in 6MWD	█%	█	█%	█%

6MWD = 6-minute walk distance; CHMP = Committee for Medicinal Products for Human Use; FC = functional class; PAH = pulmonary arterial hypertension

<sup>a</sup> Baseline rates of individual CHMP component events were sourced from the subgroup of PAH FC III/IV, no background therapy in the placebo arm of the GRIPHON trial

<sup>b</sup> Macitentan versus Placebo

<sup>c</sup> Derived by multiplying the HRs for the ITT population in SERAPHIN to the respective baseline rate in the placebo arm.

Source: Table 22, p63 of the resubmission

- 6.31 The resubmission did not provide any subgroup analyses to determine whether the hazard ratio for each endpoint was consistent across subgroups (WHO FC I/II versus III/IV). The use of the baseline rate from the GRIPHON trial rather than the SERAPHIN trial was not adequately justified.
- 6.32 The GRIPHON trial and the SERAPHIN trial were different in a number of factors that may cause heterogeneity of comparative treatment effects. It is doubtful that the application of a hazard ratio derived in the macitentan trial to the baseline risk in the selexipag trial is appropriate.

**Table 8: Results of the economic evaluation for macitentan versus placebo as monotherapy for patients with WHO FC III or IV PAH**

	Macitentan	Placebo	Increment
Costs <sup>a</sup>	\$█	\$0	\$█
Proportion of patients with hospitalisation for PAH worsening at Year 2	█%	█%	█%
<b>Incremental cost / patient with hospitalisation for PAH worsening avoided at Year 2</b>			<b>\$█</b>
Costs <sup>a</sup>	\$█	\$0	\$█
Proportion of patients with increased WHO FC at Year 2	█%	█%	█%
<b>Incremental cost / patient with increased WHO FC avoided at Year 2</b>			<b>\$█</b>
Costs <sup>a</sup>	\$█	\$0	\$█
Proportion of patients with signs/symptoms of right-sided heart failure at Year 2	█%	█%	█%
<b>Incremental cost / patient with signs/symptoms of RS heart failure avoided at Year 2</b>			<b>\$█</b>
Costs <sup>a</sup>	\$█	\$0	\$█
Number patients with ≥15% decrease in 6MWD at Year 2	█%	█%	█%
<b>Incremental cost / patient with ≥15% decrease in 6MWD avoided at Year 2</b>			<b>\$█</b>

6MWD = 6-minute walk distance; FC = functional class; PAH = pulmonary arterial hypertension; RS = right-sided; WHO = World Health Organization

<sup>a</sup> Costs were re-calculated during the evaluation an average duration of treatment of 19.0 months.

Source: Calculated during the evaluation.

The redacted table shows ICERs in the range of more than \$200,000 per incremental cost / patient with hospitalisation for PAH worsening avoided at Year 2; more than \$200,000 per incremental cost / patient with increased WHO FC avoided at Year 2; \$105,000 - \$200,000 per incremental cost / patient with signs/symptoms of RS heart

failure avoided at Year 2; and \$105,000 - \$200,000 per incremental cost / patient with  $\geq 15\%$  decrease in 6MWD avoided at Year 2.

- 6.33 For cost per patient with hospitalisation for PAH avoided, cost per patient with signs/symptoms of right-sided heart failure avoided and cost per patient with a decrease of  $\geq 15\%$  in 6MWD avoided, selexipag had a lower ICER. For cost per patient with worsening of WHO FC avoided, macitentan had a lower ICER. On this basis, the resubmission claimed that selexipag, when used as add-on therapy to an ERA and PDE-5 inhibitor in patients with WHO FC III/IV PAH, is of acceptable cost-effectiveness.
- 6.34 An ICER related to macitentan versus placebo was presented as a frame of reference for cost-effectiveness in the previous submission. The key differences in the resubmission are the standardisation of the outcomes across the trials (CHMP-defined endpoints) and the presentation of individual components of the composite outcome. The PBAC previously raised concerns regarding the comparability of the outcome definitions in GRIPHON and SERAPHIN and that the contribution of component events of varying clinical relevance may differ across the trials (paragraph 7.8, 5.11 selexipag PSD, March 2016 PBAC meeting). Notwithstanding the limitations of applying an outcome definition post hoc to trial data that was not designed to capture the outcome, the approach taken in the submission may partially address these concerns.
- 6.35 However, in March 2016 the PBAC raised other concerns regarding this approach which remain unaddressed. These are summarised below:
- Listing and circumstance of use: macitentan was recommended by the PBAC on the basis of a comparison of macitentan and bosentan for the outcome of absolute change in 6MWD, not on the basis of a composite MM endpoint and its components. The requested listing for selexipag is not consistent with macitentan's listing (add-on therapy to ERA+PDE-5 inhibitor vs monotherapy). Cost-effectiveness in the setting of monotherapy cannot necessarily be generalised to cost-effectiveness in the setting of triple (or dual) therapy (paragraph 6.39, 5.11 selexipag PSD, March 2016 PBAC meeting).
  - Clinical relevance: there was uncertainty regarding the relationship between incremental cost per first MM event per person-year prevented and the incremental cost per QALY gained (paragraphs 6.39 and 7.9, 5.11 selexipag PSD, March 2016 PBAC meeting).
  - Time horizon: the incremental effectiveness might vary over time. The time horizon of the economic evaluation cannot reflect the likely duration of treatment in the target population, which may be much longer than the 2 years (paragraph 6.39, 5.11 selexipag PSD, March 2016 PBAC meeting).

**Drug cost/patient/year: \$ [REDACTED] (public) \$ [REDACTED] (private)**

- 6.36 The cost per patient per year is based on the proposed DPMQ assuming patients receive 12.2 scripts per year. The drug cost per patient per year for the proposed effective price (based on a rebate of \$ [REDACTED] per prescription) is \$ [REDACTED] (public) and \$ [REDACTED] (private) (see Special Pricing Arrangement below).
- 6.37 As PAH is a chronic disease, treatment is intended to be ongoing.

**Estimated PBS usage & financial implications**

6.38 This resubmission was not considered by DUSC. The resubmission used a market-share approach to estimate the extent of use and financial implications associated with the listing of selexipag. This was the same approach taken in the original submission. The resubmission updated the proposed rebate from \$ [REDACTED] to \$ [REDACTED] per prescription and re-calculated the breakdown of utilisation across sectors and beneficiary types. No other changes were made to the approach.

6.39 The estimated use and financial implications are summarised in the table below.

**Table 9: Estimated use and financial implications to the PBS/RPBS**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Number of patients on PBS subsidised ERAs or PDE-5 inhibitors	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Uptake of selexipag	20%	30%	40%	45%	50%
<b>Number of patients likely to be treated</b>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Number of packs per year<sup>a</sup></b>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Net cost to the PBS/RPBS</b>					
Cost to PBS/RPBS (including co-payments)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Patient co-payments	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Net cost to the PBS/RPBS (excluding co-payments)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Proposed rebate <sup>a</sup>	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]
<b>Net cost to PBS/RPBS after rebate</b>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

ERA = endothelin receptor antagonist; PDE-5 = phosphodiesterase type 5

<sup>a</sup> Assuming 12 packs per year, as estimated by the resubmission

<sup>b</sup> The resubmission proposes a Special Pricing Arrangement in which the sponsor would rebate \$ [REDACTED] per prescription of selexipag

Source: Table compiled during the evaluation. Excel workbook “4\_Economic and financial analyses - selexipag - PAH- March 2017” supplied in the resubmission.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be \$30 - \$60 million per year.

6.40 The resubmission’s estimates did not account for the use of selexipag during the dose titration period.

**Financial Management – Risk Sharing Arrangements**

6.41 The sponsor proposed to rebate the Commonwealth of Australia \$ [REDACTED] per prescription of selexipag dispensed on the PBS under a formalised Deed of Agreement. The rebate amount was increased compared to the previous submission (when the rebate was \$ [REDACTED]).

**Other relevant issues – Proposed extension to the PBS listing of sildenafil**

- 6.42 In the Appendix to the main body of the resubmission, the sponsor requested the current PBS listing for sildenafil for use as monotherapy be extended to permit its use as add-on therapy to an ERA agent in patients who have not achieved physician-directed treatment targets. In support of the intended use of sildenafil as add-on therapy to ERAs, the sponsor conducted a systematic review and performed a meta-analysis of five clinical trials comparing PDE-5 inhibitor plus background ERA therapy with ERA alone in PAH patients. The listing of sildenafil as a component of dual second-line therapy as requested in the Appendix of the resubmission relates to a different agent and a different line of PAH therapy from the proposed listing in the main body, and therefore would require a separate major submission and full evaluation of its implications for clinical practice, health outcomes, cost-effectiveness, government health budgets, and other considerations, e.g. quality use of medicine and equity. The evidence provided in the appendix was not assessed during the evaluation. The ESC acknowledged the systematic review and meta-analysis of data on PDE-5 inhibitors provided in the appendix, but noted that the changes proposed to the sildenafil listing would have implications broader than just use in patients prescribed selexipag, and, as noted in the evaluation, would require consideration from PBAC in the form of a separate formal submission.
- 6.43 The sponsor proposed to rebate █████% of the cost of sildenafil only when it is used as an add-on to Actelion-sponsored ERA products (TRACLEER<sup>®</sup> branded bosentan and OPSUMIT<sup>®</sup> branded macitentan). The sponsor indicated that it would also be open to the extension of the listing of the other PDE-5 inhibitor, i.e. tadalafil, as proposed for sildenafil but can only offer to rebate tadalafil up to █████ for sildenafil. The sponsor indicated that this rebate would apply to sildenafil (and potentially tadalafil) used as add-on therapy to Actelion-sponsored ERA products, regardless of whether selexipag was prescribed as triple therapy or not.

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

**7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of selexipag on the PBS for the treatment of certain patients with pulmonary arterial hypertension (PAH). In reaching this conclusion, the PBAC considered that the ICERs presented in the submission remained difficult to interpret, and were highly likely to be too high to support the cost-effectiveness of selexipag in the requested listing.
- 7.2 The PBAC noted that the requested listing restricted use of selexipag to triple therapy (or dual therapy, in some situations). Whilst the PBAC acknowledged that use in this setting appeared to be most appropriate, the Committee did not necessarily consider that it would be appropriate for the PBS listing to specify triple therapy. Noting also that the approved TGA indication included monotherapy and dual therapy, as well as triple therapy, the PBAC considered that in this situation it was preferable not to specify the line of use in any listing other than as add-on therapy, and instead allow clinicians to prescribe selexipag according to their clinical judgement.

- 7.3 The PBAC remained of the view that selexipag was likely to be superior to placebo in terms of comparative effectiveness, but that the magnitude and clinical relevance of any benefit remained unclear.
- 7.4 The PBAC accepted the claim that selexipag is of inferior comparative safety compared to placebo.
- 7.5 The PBAC noted that the clinical trial results had been re-analysed in the current submission, but that the re-analysis did not change the PBAC's view of the cost-effectiveness of selexipag.
- 7.6 The PBAC noted that new clinical data for selexipag is unlikely to be forthcoming, and therefore the most likely way a more acceptable ICER could be achieved would be with a reduced proposed price.
- 7.7 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

**8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**9 Sponsor's Comment**

Actelion Pharmaceuticals Ltd will consider the comments made by the PBAC and it will seek further advice from the PBAC to decide about another re-submission requesting PBS listing of selexipag for patients with PAH.