

**5.11 SELEXIPAG,  
tablet, 200, 400, 600, 800, 1000, 1200, 1400 and 1600  
micrograms,  
Uptravi<sup>®</sup>,  
Actelion Pharmaceuticals Australia.**

**1 Purpose of Application**

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

**2 Requested listing**

2.1 The requested PBS listing is shown below. Suggestions by the Secretariat are included with suggestions and additions in *italics* and deletions in ~~strike through~~:

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)	Uptravi <sup>®</sup> Actelion
Tablet 800 microgram, 60	1	1	\$ [REDACTED] (public)	Pharmaceuticals

<b>Category / Program</b>	Section 100 – Highly Specialised Drugs Program
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	-
<b>Severity</b>	WHO Functional Class III or IV
<b>Condition</b>	Pulmonary arterial hypertension (PAH)
<b>PBS indication</b>	PAH
<b>Treatment phase</b>	Initial treatment
<b>Restriction Level / Method</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria</b>	<del>Patient must not have received prior PBS-subsidised treatment with a pulmonary arterial hypertension (PAH) agent,</del> <i>The patient must not have received prior PBS-subsidised treatment with this drug</i>  AND  Patient must have been assessed by a physician at a designated hospital,  AND  Patient must have WHO Functional Class III or IV idiopathic pulmonary arterial hypertension (iPAH), or drug or toxin-induced PAH or hereditary PAH, and a mean right atrial pressure of

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	<p>greater than 8 mmHg, as measured by right heart catheterisation (RHC); OR</p> <p>Patient must have idiopathic pulmonary arterial hypertension (iPAH), or drug or toxin-induced PAH or hereditary PAH, with right ventricular function assessed by echocardiography (ECHO) where a RHC cannot be performed on clinical grounds;</p> <p>OR</p> <p>Patient must have pulmonary arterial hypertension secondary to either: connective tissue disease; congenital heart disease with systemic-to-pulmonary shunt (including Eisenmenger's physiology); or HIV infection and a mean right atrial pressure greater than 8 mmHg, as measured by RHC;</p> <p>OR</p> <p>Patient must have WHO Functional Class III or IV pulmonary arterial hypertension secondary to either: connective tissue disease; congenital heart disease with simple systemic-to-pulmonary shunt at least 1 year after surgical repair; or HIV infection and with right ventricular function assessed by ECHO where a RHC cannot be performed on clinical grounds,</p> <p>AND</p> <p><i>The patient must have inadequate clinical response to stabilised ERA or PDE-5 inhibitor therapy</i></p> <p>AND</p> <p>The treatment must be used in combination with PBS-subsidised treatment with ambrisentan OR bosentan OR macitentan OR sildenafil OR tadalafil for pulmonary arterial hypertension (PAH).</p>
<p><b>Prescriber instructions</b></p> <p><b>Administrative Advice</b></p>	<p>Applications for authorisation must be in writing and must include:</p> <p>(1) a completed authority prescription form; and</p> <p>(2) a completed Pulmonary Arterial Hypertension PBS Authority Application - Supporting Information form which includes results from the three tests below, where available:</p> <p>(i) RHC composite assessment; and</p> <p>(ii) ECHO composite assessment; and</p> <p>(iii) 6 Minute Walk Test (6MWT); and</p> <p>(3) a signed patient acknowledgement.</p> <p>Idiopathic pulmonary arterial hypertension, drug or toxin-induced pulmonary arterial hypertension, hereditary pulmonary arterial hypertension, pulmonary arterial hypertension secondary to connective tissue disease including scleroderma, or pulmonary arterial hypertension associated with a congenital systemic-to-pulmonary shunt (including Eisenmenger's physiology) or HIV are defined as follows:</p> <p>(i) mean pulmonary artery pressure (mPAP) greater than 25 mmHg at rest and pulmonary artery wedge pressure (PAWP) less than 15 mmHg; or</p> <p>(ii) where a right heart catheter (RHC) cannot be performed on clinical grounds, right ventricular systolic pressure (RVSP), assessed by echocardiography (ECHO), greater than 40 mmHg, with normal left ventricular function.</p> <p>Test requirements to establish baseline for initiation of treatment are as follows:</p> <p>The first written application for PBS-subsidised treatment with the first PAH agent should be accompanied by the results of a right heart catheter (RHC) composite assessment plus an echocardiograph (ECHO) composite assessment, plus a 6 minute walk test (6MWT) to establish the patient's baseline measurements.</p> <p>Where it is not possible to perform all 3 tests above on clinical grounds, the following list</p>

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	<p>outlines the preferred test combination, in descending order, for the purposes of initiation of PBS-subsidised treatment:</p> <p>(1) RHC plus ECHO composite assessments;  (2) RHC composite assessment plus 6MWT;  (3) RHC composite assessment only.</p> <p>In circumstances where a RHC cannot be performed on clinical grounds, applications may be submitted for consideration based on the results of the following test combinations, which are listed in descending order of preference:</p> <p>(1) ECHO composite assessment plus 6MWT;  (2) ECHO composite assessment only.</p> <p>Where fewer than 3 tests 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.</p> <p>The test results provided must not be more than 2 months old at the time of application.</p> <p>The maximum quantity authorised will be limited to provide sufficient supply for 12 weeks of treatment, based on the dosage recommendations in the TGA-approved Product Information.</p> <p>The term 'PAH agents' refers to bosentan monohydrate, iloprost trometamol, epoprostenol sodium, sildenafil citrate, ambrisentan, tadalafil, macitentan and selexipag.</p> <p>PAH agents are not PBS-subsidised for patients with pulmonary hypertension secondary to interstitial lung disease associated with connective tissue disease, where the total lung capacity is less than 70% of predicted.</p>
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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, 60	1	5	\$ [REDACTED] (private)	Upravi Actelion
Tablet 400 microgram, 60	1	5	\$ [REDACTED] (public)	Pharmaceuticals
Tablet 400 microgram, 60	1	5		
Tablet 800 microgram, 60	1	5		
Tablet 1,000 microgram, 60	1	5		
Tablet 1,200 microgram, 60	1	5		
Tablet 1,400 microgram, 60	1	5		
Tablet 1,600 microgram, 60	1	5		

<b>Category / Program</b>	Section 100 – Highly Specialised Drugs Program
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<b>Episodicity:</b>	-
<b>Severity</b>	WHO Functional Class III or IV
<b>Condition</b>	Pulmonary arterial hypertension (PAH)
<b>PBS indication</b>	PAH
<b>Treatment phase</b>	Grandfathering selexipag patients
<b>Restriction Level / Method</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria</b>	Patient must have a documented history of WHO Functional Class III or IV idiopathic

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	<p>pulmonary arterial hypertension (iPAH), or drug or toxin-induced PAH or hereditary PAH, and a mean right atrial pressure of greater than 8 mmHg, as measured by right heart catheterisation (RHC);</p> <p>OR</p> <p>Patient must have documented history of WHO Functional Class III or IV idiopathic pulmonary arterial hypertension (iPAH), or drug or toxin-induced PAH or hereditary PAH, with right ventricular function assessed by echocardiography (ECHO) where a RHC cannot be performed on clinical grounds;</p> <p>OR</p> <p>Patient must have documented history of WHO Functional Class III or IV pulmonary arterial hypertension secondary to either: connective tissue disease; congenital heart disease with systemic-to-pulmonary shunt (including Eisenmenger's physiology); or HIV infection and a mean right atrial pressure greater than 8 mmHg, as measured by RHC;</p> <p>OR</p> <p>Patient must have documented history of WHO Functional Class III or IV pulmonary arterial hypertension secondary to either: connective tissue disease; congenital heart disease with simple systemic-to-pulmonary shunt at least 1 year after surgical repair; or HIV infection and with right ventricular function assessed by ECHO where a RHC cannot be performed on clinical grounds,</p> <p>AND</p> <p>Patient must have received treatment with <del>selexipag</del> <i>selexipag</i> this drug prior to [listing date]</p> <p>AND</p> <p>Patient must have demonstrated a response within 12 weeks of initiating treatment with this <del>agent</del> <i>drug</i> (i.e., following titration phase)</p> <p>AND</p> <p>Patient must be receiving treatment with this drug for this condition at the time of application,</p> <p>AND</p> <p>The treatment must be used in combination with on PBS-subsidised treatment with ambrisentan OR bosentan OR macitentan OR sildenafil OR tadalafil for pulmonary arterial hypertension (PAH),</p> <p>AND</p> <p>Patient must have been assessed by a physician from a designated hospital</p>
<b>Prescriber instructions</b>	<p>Applications for authorisation must be in writing and must include:  (1) a completed authority prescription form; and</p>

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<b>Administrative Advice</b>	<p>(2) a completed Pulmonary Arterial Hypertension PBS Authority Application - Supporting Information form</p> <p>The maximum quantity authorised will be limited to provide sufficient supply for 1 month of treatment, based on the dosage recommendations in the Therapeutic Goods Administration (TGA) approved Product Information.</p> <p>A maximum of 5 repeats will be authorised.</p> <p>Applications for continuing treatment with a PAH agent should be made prior to the completion of the 6 month treatment course to ensure continuity for those patients who respond to treatment, as assessed by the treating physician.</p> <p>The term 'PAH agents' refers to bosentan monohydrate, iloprost trometamol, epoprostenol sodium, sildenafil citrate, ambrisentan, tadalafil, macitentan and selexipag.</p> <p>PAH agents are not PBS-subsidised for patients with pulmonary hypertension secondary to interstitial lung disease associated with connective tissue disease, where the total lung capacity is less than 70% of predicted.</p>
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<b>Category / Program</b>	Section 100 – Highly Specialised Drugs Program
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	-
<b>Severity</b>	WHO Functional Class III or IV
<b>Condition</b>	Pulmonary arterial hypertension (PAH)
<b>PBS indication</b>	PAH
<b>Treatment phase</b>	Continuing treatment (all patients)
<b>Clinical criteria</b>	<p>Patient must have received approval for initial PBS-subsidised treatment with this <del>agent</del> drug,</p> <p>AND</p> <p>Patient must have demonstrated a response within 12 weeks of initiating treatment with this <del>agent</del> drug,</p> <p>AND</p> <p>The treatment must be used in combination with PBS-subsidised treatment with ambrisentan OR bosentan OR macitentan OR sildenafil OR tadalafil for pulmonary arterial hypertension (PAH),</p> <p>AND</p> <p>Patient must have been assessed by a physician from a designated hospital</p>
<b>Prescriber instructions</b> <b>Administrative Advice</b>	<p>Applications for authorisation must be in writing and must include:</p> <p>(1) a completed authority prescription form; and</p> <p>(2) a completed Pulmonary Arterial Hypertension PBS Authority Application - Supporting Information form</p> <p>The maximum quantity authorised will be limited to provide sufficient supply for 1 month of treatment, based on the dosage recommendations in the Therapeutic Goods Administration (TGA) approved Product Information.</p>

	<p>A maximum of 5 repeats will be authorised.</p> <p>Applications for continuing treatment with a PAH agent should be made prior to the completion of the 6 month treatment course to ensure continuity for those patients who respond to treatment, as assessed by the treating physician.</p> <p>The term 'PAH agents' refers to bosentan monohydrate, iloprost trometamol, epoprostenol sodium, sildenafil citrate, ambrisentan, tadalafil, macitentan and selexipag.</p> <p>PAH agents are not PBS-subsidised for patients with pulmonary hypertension secondary to interstitial lung disease associated with connective tissue disease, where the total lung capacity is less than 70% of predicted.</p>
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- 2.2 In contrast to the restrictions for all currently listed PAH agents, in which patients are only eligible for one PBS-subsidised PAH agent at any time, the proposed restriction for selexipag specified that it must be used in combination with other PBS-subsidised PAH drugs (an endothelin receptor agonist (ERA) and/or a phosphoesterase type 5 (PDE-5) inhibitor).
- 2.3 The submission stated that selexipag was intended to be used as “add-on therapy in patients stabilised on background therapy with an ERA and/or a PDE-5 inhibitor but who have not achieved physician-directed treatment targets.”
- The proposed restriction for ‘Initial treatment (new patients)’ would allow for a new patient to be commenced on dual therapy;
  - The restriction does not specify that patients must have had inadequate response to stabilised ERA or PDE-5 inhibitor therapy to be eligible for selexipag, nor does it define what constitutes an inadequate response. In the absence of such criteria, there would be considerable potential for use outside the intended patient population.
- 2.4 The requested restriction is not consistent with the proposed TGA indication. The TGA documents received with the PSCR indicate that selexipag will be registered for use in combination with an ERA or a PDE-5 inhibitor, or in triple combination with an ERA and a PDE-5 inhibitor, or as monotherapy. The clinical justification for the PBS listing being more restrictive than the TGA registration was unclear. The PBAC considered that the hearing was helpful in clarifying the likely use of selexipag should it be listed on the PBS.
- 2.5 A grandfathering restriction for initial treatment was also proposed in the submission for patients currently receiving selexipag in the extension phase of a clinical trial or as part of a patient familiarisation program.

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

### **3 Background**

- 3.1 The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, the ACPM outcome for selexipag was available.
- 3.2 According to the draft PI, selexipag will be indicated for the treatment of:
- 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<sup>12/19</sup>
- pulmonary arterial hypertension associated with drugs and toxins in patients with WHO functional class II, III or IV symptoms.

UPTRAVI is effective in combination with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor, or in triple combination with an ERA and a PDE-5 inhibitor, or as monotherapy.

- 3.3 This was the first submission to the PBAC for listing of selexipag for treatment of PAH. The submission requested listing of selexipag as add-on treatment in PAH patients who are already receiving a PBS-subsidised PAH agent, i.e. it requested PBS-subsidy for combination therapy.
- 3.4 As of January 2016, PBS subsidy was available for the following medicines specifically for WHO FC III and/or IV PAH: bosentan, iloprost, epoprostenol, sildenafil, ambrisentan, tadalafil and macitentan. Under the current restrictions for PAH drugs, patients are only eligible for PBS subsidised treatment with one PAH agent at any time.
- 3.5 In February 2015 the Drug Utilisation Sub-Committee (DUSC) conducted a PAH medicines utilisation analysis (Item 7.3 DUSC February 2015). The DUSC considered that the PBS restriction for PAH agents was not consistent with current treatment guidelines in that;
- It required failure to respond to 6 or more weeks of appropriate vasodilator treatment for WHO FC III patients with a mean right atrial pressure of 8 mmHg or less;
  - It did not allow treatment of WHO FC II patients; and
  - It did not allow combination therapy.
- 3.6 The PBAC previously considered that there were a number of issues around use of PAH agents that could not be assessed within the scope of the submission, including:
- The lack of evidence to support cost-effectiveness of combination therapy of PAH agents, as is claimed to occur in practice (currently only one PBS-subsidised PAH agent may be used at a time); and
  - The lack of evidence to support cost-effectiveness for use in New York Heart Association Functional class (NYHA FC) II patients; and
  - The difficulty in identifying the population of patients who derive the most benefit from these agents.

In this regard, the PBAC recommended that a Post-Market Review of the efficacy and cost-effectiveness of agents for the treatment of PAH, including the existing listing for class III and class IV patients, and the additional clinical place of these therapies recommended in international guidelines (Item 6.8 Bosentan, epoprostenol and macitentan Public Summary Document (PSD), July 2015 PBAC Meeting).

- 3.7 In July 2015, a minor submission to the PBAC requested changes to the current ‘continuing treatment’ restriction of bosentan, epoprostenol and macitentan to remove the requirement that:
- i) The patient must have been assessed as having achieved a response to their most recent course of treatment; and
  - ii) Clinicians must provide evidence that a patient has been assessed as having achieved response when wanting to prescribe continued treatment.

The PBAC noted the submission’s claim that the current PBS continuing restriction was inconsistent with best clinical practice (Item 6.8 Bosentan, epoprostenol and macitentan PSD, July 2015 PBAC Meeting). The PBAC recommended the following amendments to the PBS restrictions for bosentan, epoprostenol and macitentan:

- No changes to the initial treatment restriction;
- That the current “continuing treatment (all patients)” restriction be replaced by the following:
  - a “continuing treatment – new patient” phase (written authority), which would retain the same criteria as the existing “continuing” treatment restriction (i.e. patient will need to demonstrate a response to the initial course of treatment); and
  - a “continuing treatment – beyond initial 48 weeks of treatment” phase (telephone authority), which would be as requested by the submission – an amended version of the current continuing treatment restriction, removing requirements to provide evidence of a response to the most recent course of treatment with the agent.

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

- 4.1 PAH is a rare, severe progressive clinical condition characterised by a sustained elevation of pulmonary vascular resistance, which ultimately leads to right heart failure and death.

There are currently three classes of PAH agents which act by means of three different mechanisms that target the mediators of the main biologic pathways in the pathogenesis of PAH: ERAs, PDE-5 inhibitors, and prostacyclin analogues. In patients who have inadequate response to monotherapy, current clinical guidelines recommend using agents targeting the different pathways in sequential combination with each other (i.e. double or triple sequential combination therapy).

- 4.2 The DUSC review of PAH noted that:
- Until mid-2014, bosentan was the most frequently prescribed first PAH medicine. Macitentan has become the most common medicine for new patients since it was listed on 1 September 2014; patients rarely initiate PAH therapy on iloprost or epoprostenol;
  - In practice, combination therapy is achieved by adding low cost private script sildenafil (a PDE-5 inhibitor) to another of the PBS subsidised drugs.
- 4.3 The submission proposed PBS listing of selexipag for use as add-on therapy to ERAs or PDE-5 inhibitors, and anticipated that most of the use of selexipag would be in patients already on dual combination background therapy with an ERA and PDE-5 inhibitor. The requested listing for selexipag does not restrict the use of selexipag to

triple-therapy, but also allows for its use as a component of dual therapy in combination with either an ERA or a PDE-5 inhibitor.

- 4.4 If selexipag is recommended for listing, it would be the only PAH agent PBS-subsidised for combination therapy. As such, it may replace the use of a PDE-5 inhibitor (non-PBS subsidised) as add-on therapy in patients who have a sub-optimal response to monotherapy with an ERA (PBS-subsidised), and vice-versa. Selexipag is also likely to replace much of the current use of iloprost and epoprostenol as add-on therapies to ERAs and/or PDE-5 inhibitors, as it would be the only PAH drug acting on the prostacyclin pathway that is available in tablet form.

The submission has not addressed the comparative safety and effectiveness of selexipag, when used as add-on therapy, versus PAH agents currently being used for this purpose in clinical practice.

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

## **5 Comparator**

- 5.1 Due to the discrepancy between the current PBS restrictions for PAH-specific drugs and current clinical practice, defining the appropriate comparator(s) is difficult.
- 5.2 The submission nominated placebo (as add-on to current therapy) as the comparator. The availability of PBS-subsidised add-on therapy is likely to expand the current market for combination therapy, as it is likely to increase the proportion of PAH patients receiving combination therapy and patients may commence combination therapy at an earlier stage of disease progression. Therefore, placebo is an appropriate comparator.
- 5.3 While there is considerable uncertainty in the current extent of use of add-on therapy in clinical practice and the specific drugs being used, the PBAC may wish to consider whether non-PBS subsidised PAH-agents currently being used for this purpose may also be relevant comparators.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the current clinical management of patients, including use of currently subsidised treatments and how patients are assessed for clinical response in practice. The clinician also discussed how the drug would likely be used in practice, noting that although selexipag would provide access to a class of treatment (prostacyclin analogue) that is currently not broadly used, (largely due to safety/tolerability and barriers of administration) selexipag was likely to be reserved for use in third line, after patients had tried treatment with ERAs and PDE-5 inhibitors. The clinician also addressed other matters in response to the Committee's questions. The PBAC considered that

the hearing was informative in clarifying the likely use of selexipag in clinical practice.

### Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (3), health care professionals (2) and organisations (1) via the Consumer Comments facility on the PBS website. The comments noted that subsidy for combination therapy would be in line with International treatment Guidelines, and described benefits including slowing of progression of disease and the impact this would have on patients' quality of life.
- 6.3 The PBAC noted the input received from the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ) clarifying the likely use of selexipag in clinical practice. The PBAC specifically noted the advice that PHSANZ would support the use of selexipag as additional therapy in patients already on at least monotherapy or already receiving combination therapy, but did not think use as monotherapy would be appropriate. The advice from PHSANZ also noted the issues associated with combination therapy not being funded by the PBS, including inequality of access to therapy.

### Clinical trials

- 6.4 The submission was based on one head-to-head trial comparing selexipag, with or without background PAH-specific therapy (either an ERA or a PDE-5 inhibitor), to placebo, with or without background PAH-specific therapy (referred to as BGT), (n=1,156).
- 6.5 Details of the trials 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, et al. Selexipag for the treatment of pulmonary arterial hypertension.	March 2014  New England Journal of Medicine 2015; 373 (26):2522-2533

Source: Table B.2-2, p63 of the submission

6.6 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 Organisation 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: compiled during the evaluation

6.7 In the key randomised controlled trial (GRIPHON):

- 46% of patients had WHO FC I or II PAH, and 20% were not receiving any PAH-specific medications at baseline (i.e. they received selexipag monotherapy in the trial). The trial ITT population was, therefore, not representative of the eligible population under the requested listing; and
- Less than 1% of patients (N = 11) had WHO FC IV PAH.

6.8 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 end-points:

- 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 (Macitentan PSD, March 2014 PBAC meeting).

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

- Patients who experienced a non-fatal primary endpoint event were permitted to discontinue double-blind treatment and were eligible to receive treatment with open-label selexipag. Patients were not followed for subsequent morbidity events. Consequently, survival data for each morbidity component of the primary outcome are not available and the secondary outcome of overall survival up to study closure was confounded by patients switching from placebo to selexipag; and
- Patients who discontinued treatment early (before study closure) without a

primary outcome event, including for reasons such as discontinuation due to adverse events (AEs), 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 ± 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.

### **Comparative effectiveness**

- 6.10 Table 3 summarises the results for ITT analysis of time to first CEC-confirmed MM event up to EOT plus 7 days. Overall, the ESC considered that the composite outcome was difficult to interpret. In particular, the ESC questioned:
- The difference between some of the MM events.
  - Whether patients could have more than one 'first' MM event, and in this case, how the decision was made to assign patients to a particular event.
- 6.11 The Pre-PBAC Response clarified that only the first occurring event was counted, and that if a patient experienced more than one event concurrently, the patient was classified to the most severe event type. The order of severity of events from most severe to least severe was death (any cause); hospitalisation for worsening of 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 of PAH; disease progression.

Overall, the ESC considered that the use of a composite where death has the same clinical relevance as hospitalisation is not informative.

**Table 3: First CEC-confirmed MM event up to EOT plus 7 days in the GRIPHON trial (ITT)**

	<b>Selexipag ± BGT N=574 n (%)</b>	<b>Placebo ± BGT N=582 n (%)</b>
Median duration of follow-up, weeks (IQR) <sup>a</sup>	70.7 (32.0, 117.1)	63.7 (28.6, 107.1)
<b>Patients with CEC-confirmed first MM event to EOT+7 days</b>	155 (27.0%)	242 (41.6%)
Hazard ratio (99% CI); 1-sided stratified log-rank p-value <sup>b</sup>	0.60 (0.46, 0.78) <0.0001	
<b>Component outcomes<sup>c</sup></b>		
Death all causes	28 (4.9%)	18 (3.1%)
Hospitalisation for PAH worsening	78 (13.6%)	109 (18.7%)
Parenteral prostanoid or chronic oxygen therapy	10 (1.7%)	13 (2.2%)
Lung transplantation or balloon atrial septostomy	1 (0.2%)	2 (0.3%)
Disease progression <sup>d</sup>	38 (6.6%)	100 (17.2%)

BGT = background therapy; CEC = Critical Event Committee; CI = confidence interval; EOT = end-of-treatment; IQR = interquartile range; ITT = intention-to-treat; MM = morbidity or mortality; PAH = pulmonary arterial hypertension

<sup>a</sup> Safety analysis set

<sup>b</sup> Group sequential efficacy boundary for the primary analysis: one-sided p-value ≤0.00499.

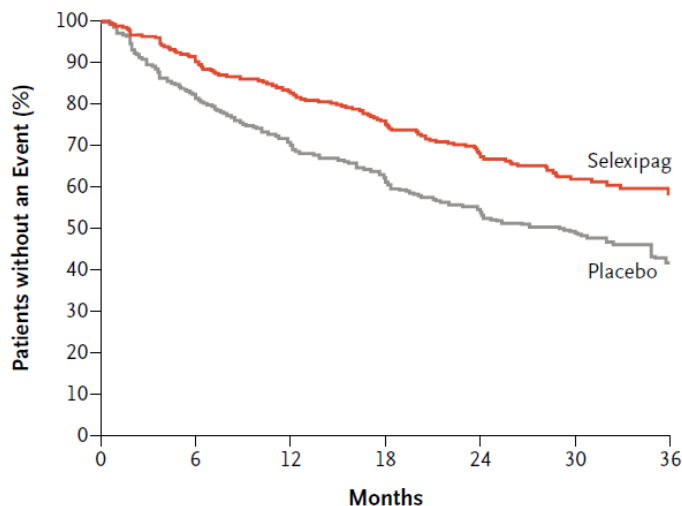
<sup>c</sup> Survival data for component outcomes were not available as patients were only followed up to 7 days after end of treatment.

<sup>d</sup> The submission did not provide a breakdown of disease progression events and this information could not be located in the GRIPHON CSR.

Source: Table B.6-1, p 84 of the submission

- 6.12 The beneficial effect of selexipag ± BGT over placebo ± BGT was due to both a difference in disease progression (decrease in 6MWD from baseline plus either worsening of WHO FC or need for additional PAH specific therapy), and a lower rate of hospitalisation for worsening of PAH in the selexipag ± BGT arm compared to the placebo ± BGT arm. There was no evidence that selexipag had a statistically significant effect on overall survival.

**Figure 1: Time to first MM event**

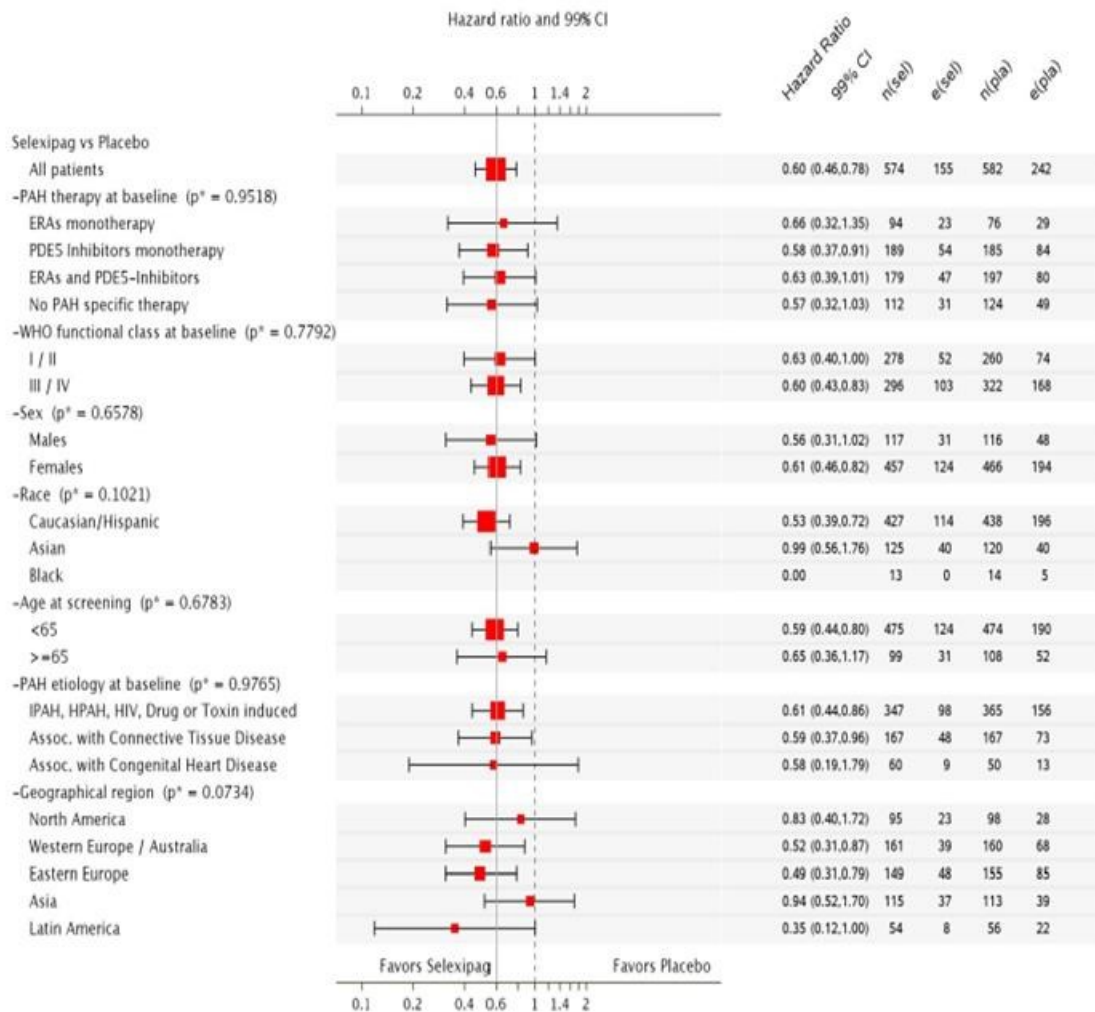


No. at Risk							
Placebo	582	433	347	220	149	88	28
Selexipag	574	455	361	246	171	101	40

Source: N Engl J Med 2015;373:2522-33. DOI: 10.1056/NEJMoa1503184

- 6.13 Death from any cause, up to study closure, occurred in 17.4% and 18.0% of patients in the selexipag ± BGT and the placebo ± BGT arms, respectively (HR 0.97; 95%CI: 0.74, 1.28). This outcome was potentially confounded in favour of placebo, as 27% of patients from the placebo group swapped to selexipag treatment after experiencing a non-fatal first MM event. The results of a sensitivity analysis in which patients with missing survival status data (4.4% and 5.2% of patients in the selexipag and placebo groups, respectively) were assumed to have died, were consistent with the main analysis (HR 0.95; 95% CI 0.74, 1.21).
- 6.14 The submission only requested listing of selexipag for patients with WHO FC III or IV PAH. In addition, the restriction precluded the use of selexipag as monotherapy. The forest plot for the subgroup analyses for the primary outcome in the GRIPHON trial are presented in Figure 2.

Figure 2: Time to first CEC-confirmed MM event up to EOT + 7 days, forest plot for subgroups



\* = Interaction p-value. n(sel) = No. patients in Selexipag. e(sel) = No. patients with event in Selexipag. n(pla) = Number of patients in Placebo. e(pla) = No. patients with event in Placebo.

Note: Race group Other is not displayed in analysis, as the population is less than 20. The vertical solid line references the overall treatment effect. Events with CEC-confirmed onset date up to 16 Aug 2011 are included as events.

Figure FMMTGRP\_F - Produced by zeeja1 on 28JUL14 - Data dump of 12JUN2014

CEC = Critical Event Committee; EOT = end-of-treatment; ERA = endothelin receptor antagonist; HIV = human immunodeficiency virus; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; WHO = World Health Organisation

Source: Figure B.6-6, p88 of the submission

- 6.15 Results for the subgroup of PAH patients for whom listing of selexipag was requested, namely patients with WHO FC III/IV patients who were receiving PAH-specific therapy at baseline, were not provided. However, individually the WHO FC and background therapy did not appear to significantly affect the HR for the primary outcome.
- 6.16 The interpretation of the subgroup analyses was complicated by the fact the composite outcome included components of varying clinical relevance. The relative contribution of each component endpoint may have differed between subgroups.

- 6.17 Comparative outcomes for MM component events experienced subsequent to the first outcome event were not available, as patients who experienced a non-fatal primary endpoint event were permitted to discontinue double-blind treatment and were eligible to receive treatment with open-label selexipag.
- 6.18 The effect of selexipag on the individual components of the composite end point appeared to vary, with the benefit largely driven by hospitalisations and increased treatment, rather than changes in disease progression or death. Given the side effect profile of selexipag and the potential for unblinding, combined with the subjective nature of some of these outcomes, some of the differences observed may be explainable due to (outcome) measurement bias.

### **Comparative harms**

- 6.19 The interpretation of the number of patients experiencing AEs was complicated by the fact the some of the AEs reported during the trial were likely to be indicators of disease progression, rather than drug-related effects.
- 6.20 The most frequently reported AEs were typical of those generally associated with prostacyclins (headache, diarrhoea, nausea, pain in jaw, myalgia, pain in extremity, vomiting and flushing), all of which occurred with greater frequency in the selexipag ± BGT group compared to the placebo ± BGT group (Table 4). Prostacyclin-associated AEs (including headache, diarrhoea, nausea, pain in extremity, myalgia, dizziness and vomiting) led to discontinuation of study drug in 10.3% and 1.9% of patients randomised to selexipag ± BGT and placebo ± BGT, respectively (Table 12-10, p 273 GRIPHON Clinical Study report (CSR)). The ESC noted from the PSCR (p4) that the maintenance dose of study drug for each patient was determined by up-titrating patients to the point at which the patient experienced adverse effects and then back-titrating one step. Overall, the ESC noted that the pattern of AEs was similar in the titration and maintenance phases

**Table 4: Summary of treatment-emergent AEs occurring in ≥5% of patients in at least one arm of the GRIPHON trial, sorted by difference in incidence between selexipag and placebo (SAF)**

	Selexipag ± BGT N=575	Placebo ± BGT N=577	Absolute difference (95%CI)
Duration of study treatment (weeks) Median (range)	70.7 (0.3 - 216.7)	63.7 (0.7 - 192.0)	
Headache*	375 (65.2%)	189 (32.8%)	32.5% (27.0%, 37.9%)
Diarrhoea*	244 (42.4%)	110 (19.1%)	23.4% (18.2%, 28.5%)
Pain in jaw*	148 (25.7%)	36 (6.2%)	19.5% (15.4%, 23.6%)
Nausea*	193 (33.6%)	107 (18.5%)	15.0% (10.0%, 20.0%)
Myalgia*	92 (16.0%)	34 (5.9%)	10.1% (6.5%, 13.7%)
Vomiting*	104 (18.1%)	49 (8.5%)	9.6% (5.7%, 13.5%)
Pain in extremity*	97 (16.9%)	46 (8.0%)	8.9% (5.1%, 12.7%)
Flushing*	70 (12.2%)	29 (5.0%)	7.1% (3.9%, 10.4%)
Arthralgia*	62 (10.8%)	44 (7.6%)	3.2% (-0.2%, 6.5%)
Anaemia	48 (8.3%)	31 (5.4%)	3.0% (0.1%, 5.9%)
Abdominal pain	48 (8.3%)	33 (5.7%)	2.6% (-0.3%, 5.6%)
Decrease appetite	34 (5.9%)	19 (3.3%)	2.6% (0.2%, 5.0%)
Nasopharyngitis	75 (13.0%)	63 (10.9%)	2.1% (-1.6%, 5.9%)
Hypotension	29 (5.0%)	18 (3.1%)	1.9% (-0.4%, 4.2%)
Asthenia	31 (5.4%)	24 (4.2%)	1.2% (-1.2%, 3.7%)

AE = adverse event; BGT = background therapy; CI = confidence interval; SAF = safety analysis set

\* AEs associated with prostacyclins

95% confidence intervals were calculated during the evaluation

Source: Table 12-1, p255 and Table 12-4, p261 of the submission.

- 6.21 Deaths up to EOT plus 7 days that were adjudicated as not PAH-related by the CEC occurred in 2.3% and 1.7% of patients in the selexipag ± BGT and placebo ± BGT groups, respectively. In the safety analysis set (SAF), a total of 49 (8.5%) and 41 (7.1%) patients in the selexipag ± BGT and placebo ± BGT groups, respectively, experienced at least 1 serious AE (SAE) up to EOT plus 7 days with subsequent fatal outcome. There was no association between the number of SAEs with fatal outcome and the selexipag dose (p266 GRIPHON CSR). The most frequently reported SAEs with fatal outcome were worsening of PAH and right ventricular failure; other causes included sudden death, cardiopulmonary failure and cardiac arrest.

### **Benefits/harms**

- 6.22 A summary of the comparative benefits and harms for selexipag ± BGT versus placebo ± BGT is presented in the table below.

**Table 5: Summary of comparative benefits and harms for selexipag ± BGT and placebo ± BGT in the GRIPHON trial**

<b>Benefits</b>						
<b>Time to first CEC-confirmed MM event: GRIPHON</b>						
	<b>Selexipag ± BGT</b>	<b>Placebo ± BGT</b>	<b>HR (99% CI)*</b>			
<b>ITT analysis</b>						
Patients with event**	155/574	242/582	0.60 (0.46, 0.78)			
Median time to first MM event	NA <sup>a</sup>	NR				
<b>Subgroup analyses</b>						
WHO functional class						
I/II	52/278 (18.7%)	74/260 (28.5%)	0.63 (0.40, 1.00)			
III/IV	103/296 (34.8%)	168/322 (52.2%)	0.60 (0.43, 0.83)			
PAH therapy at baseline						
ERA monotherapy	23/94 (24.5%)	29/76 (38.2%)	0.66 (0.32, 1.35)			
PDE-5i monotherapy	54/189 (28.6%)	84/185 (45.4%)	0.58 (0.37, 0.91)			
ERA+PDE-5i	47/179 (26.3%)	80/197 (40.6%)	0.63 (0.39, 1.01)			
No PAH therapy	31/112 (27.7%)	49/124 (39.5%)	0.57 (0.32, 1.03)			
<b>Harms</b>						
	<b>Selexipag ± BGT</b>	<b>Placebo ± BGT</b>	<b>RR (95% CI)</b>	<b>Event rate/100 patients**</b>		<b>RD (95% CI)</b>
				<b>Selexipag ± BGT</b>	<b>Placebo ± BGT</b>	
<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>b</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%)

AE = adverse event; BGT = background therapy; CEC = Critical Event committee; CI = confidence interval; ERA = endothelin receptor antagonist; HR = hazard ratio; ITT = intention-to-treat; MM = morbidity or mortality; NA = not available; NR = not reported; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type 5 inhibitor; RD = risk difference; RR = risk ratio

\* Group sequential efficacy boundary for the primary analysis: one-sided p-value ≤0.00499.

\*\* Median duration of exposure: 70.7 weeks in the selexipag arm and 63.7 weeks in the placebo arm

<sup>a</sup> The median time to first event was not available for the selexipag ± BGT treatment arm which was not yet mature.

<sup>b</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

6.23 On the basis of direct evidence presented by the submission, for every 100 patients treated with selexipag ± BGT in comparison to placebo ± BGT;

- Approximately 15 less patients would have experienced a MM event in the first 64 weeks of treatment;
- Approximately 7 additional patients would discontinue treatment due to an AE not classified as PAH progression over a median duration of exposure of 64 - 71 weeks;
- Approximately 8 additional patients would discontinue treatment due to a prostacyclin-associated AE over a median duration of exposure of 64 - 71 weeks;

### **Clinical claim**

- 6.24 The submission described selexipag as superior to placebo in terms of comparative effectiveness and inferior in terms of comparative safety over placebo, as add-on therapy for the treatment of patients with WHO FC III or IV PAH.
- 6.25 This claim was reasonable in terms of comparative safety.
- 6.26 Selexipag ± BGT was statistically significantly superior to placebo ± BGT in terms of the composite primary outcome in patients with WHO FC I-IV PAH, who are either naïve to or receiving PAH-specific treatment at baseline (the ITT population). However, this population does not match the proposed listing.
- 6.27 In terms of evidence supporting superior effectiveness compared to placebo for the proposed PBS population there were the following concerns:
- No results for patients with WHO FC III/IV who are also receiving PAH-specific therapy at baseline were provided;
  - Very sparse data for FC IV (1% of participants)
  - There was no difference in the primary outcome for patients on ERA monotherapy at baseline (although this may have been due to lack of statistical power);
  - The beneficial effect of selexipag ± BGT compared to placebo ± BGT was driven by the lower rates of disease progression (primarily due to add on therapy) and hospitalisation for worsening of PAH. There was no evidence that selexipag ± BGT had an effect on overall survival;
  - There was minimal evidence for the comparative effectiveness of selexipag ± BGT in patients with WHO FC IV (n=11); and
  - Sensitivity analyses indicated that censoring of patients who discontinued treatment prematurely biased the treatment effect estimates in favour of selexipag.
- 6.28 In support of the claim, the observed treatment effect for the primary outcome appeared reasonably consistent across the majority of subgroups examined in the trial.
- 6.29 The submission did not present any evidence for the comparative effectiveness and safety of selexipag, when used as add-on therapy, versus other PAH-agents (non-PBS subsidised) that are currently being used for this purpose in clinical practice.
- 6.30 The PBAC considered that the claim of superior effectiveness over placebo (as add-on to current therapy) was probably reasonable. However, the magnitude of benefit, and the clinical significance of this benefit, remained unclear.

### **Economic analysis**

- 6.31 The submission presented a trial-based cost-effectiveness analysis, in which the incremental effectiveness was measured in terms of the reduction in the number of first MM events<sup>\*</sup> per person-year over the duration of the trial (referred to in the

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<sup>\*</sup> Throughout the economic evaluation first MM events are those reported up to end-of-treatment plus 7 days, as measured for the primary outcome of the GRIIPHON trial.

submission as the MM event rate per person-year), i.e. the incremental cost-effectiveness ratio (ICER) was the incremental cost per unit reduction in the number of first MM events per person-year.

- 6.32 The submission did not extrapolate either costs or health outcomes beyond the duration of the trial. As PAH is a chronic condition, the time horizon over which the outcomes were determined did not capture the long-term effectiveness or costs of treatment. The health outcome used in the economic evaluation also did not capture subsequent MM events in patients experiencing non-fatal first MM events.
- 6.33 The population used in the economic evaluation was the subgroup of patients with WHO FC III/IV PAH in the GRIPHON trial. The population in the model was not representative of the population for whom PBS listing is sought, in that 14% of the WHO FC III/IV subgroup were not receiving background PAH therapy. In addition patients were on average younger than the PBS population.

Healthcare costs

- 6.34 The only healthcare cost considered in the economic evaluation was the cost of selexipag. The economic evaluation was based on the proposed effective price for selexipag.

Health outcomes

- 6.35 The submission estimated the incremental treatment effect of selexipag compared to placebo, in terms of the reduction in the number of first MM events per person-year over the duration of the trial, based on the HR for the ITT population and the baseline event rate for the subgroup of patients with WHO FC III/IV PAH (i.e. the number of events per person-year in the placebo arm). The results are summarised in Table 6.

**Table 6: Incremental health outcome obtained in the economic evaluation (WHO FC III/IV subgroup)**

	Selexipag ± BGT	Placebo ± BGT	Incremental outcome**
Number of first MM events per person-year*			-

BGT = background therapy; MM = morbidity or mortality; WHO FC = World Health Organisation Functional class

\* Over the duration of the GRIPHON trial

\*\* Incremental change in number of first MM events per person-year over the duration of the trial.

Source: Table D.1-3, p96 of the submission.

- 6.36 The following factors are likely to have resulted in an overestimate of the difference in first MM event rates per person-year for selexipag versus placebo compared with what is likely to be observed in the Australian clinical setting:
- Data presented in the trial CSR indicated a declining difference in the first MM event rate between the treatment arms following the first 6 months of treatment;
  - The inclusion of patients who were not receiving background PAH therapy, and who would thus not be eligible for treatment according to the proposed listing; and,
  - The difference in the rate of premature censoring across the treatment arms biased the estimated treatment effect in favour of selexipag.

Incremental costs and effectiveness

6.37 The results of the economic evaluation for selexipag compared to placebo are summarised in Table 7.

**Table 7: Results of the economic evaluation for selexipag versus placebo as add-on therapy in patients with WHO FC III/IV PAH**

Component	Selexipag	Placebo	Increment
Costs <sup>a</sup>			
Proposed effective price <sup>b</sup>	\$ [REDACTED]	\$0	\$ [REDACTED]
Number of first MM events per person-year	[REDACTED]	[REDACTED]	- [REDACTED]
<b>Incremental cost/first MM event per person-year prevented*</b>			<b>\$ [REDACTED]</b>

DPMQ = dispensed price for maximum quantity; MM = morbidity or mortality; PAH = pulmonary arterial hypertension; WHO FC = World Health Organisation Functional class

<sup>a</sup> Weighted cost based on 23% private and 77% public. <sup>b</sup> The submission proposed a Special Pricing Arrangement in which the sponsor would provide a rebate of \$ [REDACTED] per prescription of selexipag.

\* Over the duration of the trial

Source: Table D.1-3, p96 of the submission; costs were recalculated during the evaluation.

6.38 To assist in the interpretation of this ICER, the submission provided a frame of reference for the acceptability of the ICER obtained for selexipag over placebo, by providing the incremental cost per incremental reduction in the rate of first MM events for macitentan when used as monotherapy in the population for whom macitentan is PBS listed, i.e. the population in which the PBAC considered that the cost-effectiveness of macitentan was acceptable. The data for this analysis were sourced from the SERAPHIN trial, which was included as the key trial in the March 2014 macitentan submission to the PBAC.

6.39 The ESC acknowledged that the ‘frame of reference’ was provided to give context to the ICER, and agreed that in some cases this approach would assist in the interpretation of the economic evaluation, in particular where results were not able to be presented in terms of survival or quality of life. However, in this case the ESC considered that the comparison of the selexipag ICER with the ‘corresponding’ macitentan ICER was not appropriate or informative.

- Macitentan was recommended for listing for use as monotherapy in patients with WHO FC III/IV PAH on the basis of non-inferiority to bosentan for the outcome of 6MWD (Macitentan PSD, March 2014 PBAC meeting). The requested restriction for selexipag is not consistent with macitentan’s current restriction. Cost effectiveness in this setting can not necessarily be generalised to use in combination
- No information was provided as to how well the incremental cost per incremental reduction in the number of first MM events per person-year would map to the incremental cost per quality-adjusted life-year (QALY) gained; and
- The incremental effectiveness, in terms of the difference in the number of first MM events per person-year, may vary over time. Therefore, unless the incremental effectiveness is determined over the likely duration of treatment in the target population, it is both difficult to interpret, and of limited external applicability. Given the chronic nature of PAH, treatment is likely to be life-long.

- 6.40 The approach taken to estimate the incremental treatment effect of macitentan compared to placebo was the same as that used for selexipag. Consistent with that presented for selexipag, data presented in the SERAPHIN CSR indicated that the difference in the number of first MM events per person-year between the treatment arms decreased after the first 6 months of treatment.
- 6.41 The following table compares the results for time to first MM event in the GRIPHON (selexipag) and SERAPHIN (macitentan) studies. The ESC noted that the definitions of the MM events were not entirely consistent between the selexipag and macitentan studies.

**Table 8: Comparison of results for time to first CEC-confirmed MM event in the GRIPHON and SERAPHIN trials, ITT analysis.**

	GRIPHON		SERAPHIN	
	Selexipag ± BGT N=574 n (%)	Placebo ± BGT N=582 n (%)	Macitentan ± BGT N=242 n (%)	Placebo ± BGT N=250 n (%)
Duration of follow-up (weeks)	70.7	63.7	118.4	101.3
Median (interquartile range)	(32.0, 117.1)	(28.6, 107.1)	(60.0, 144.0)	(30.0, 128.9)
<b>Patients with CEC-confirmed MM event</b>	155 (27.0%)	242 (41.6%)	76 (31.4%)	116 (46.4%)
Hazard ratio	0.60 (99% CI: 0.46, 0.78)		0.55 (97.5% CI: 0.39, 0.76)	
Log-rank p-value	p<0.0001		p<0.0001	
<b>Component outcomes<sup>a</sup></b>				
Death all causes <sup>b</sup>	28 (4.9%)	18 (3.1%)	16 (6.6%)	17 (6.8%)
Hospitalisation for PAH worsening	78 (13.6%)	109 (18.7%)	Not included as separate component	
Parenteral prostanoid or chronic oxygen therapy / IV or SC prostanoids <sup>c</sup>	10 (1.7%)	13 (2.2%)	1 (0.4%)	6 (2.4%)
Lung transplantation or balloon atrial septostomy <sup>c</sup>	1 (0.2%)	2 (0.3%)	-	-
Disease progression / Other worsening of PAH	38 (6.6%)	100 (17.2%)	59 (24.4%)	93 (37.2%)

Source: Table B.6-1, p 84 of the submission; Table 12-1, p 255 GRIPHON CSR; p 129, Table 20, p 132, and Table 38, p181 SERAPHIN CSR.

BGT = background therapy; CEC = Critical Event Committee; CI = confidence interval; ITT = intention-to-treat; IV = intravenous; MM = morbidity or mortality; PAH = pulmonary arterial hypertension; SC = subcutaneous

<sup>a</sup> See Table C.1.2.6 for definitions

<sup>b</sup> GRIPHON: death up to end-of-treatment + 7 days; SERAPHIN: death or onset of a treatment emergent AE with a fatal outcome within 4 weeks of end-of-treatment.

<sup>c</sup> Including hospitalisation for event

- 6.42 The results of the estimated ICER for macitentan compared to placebo are summarised in Table 9.

**Table 9: Results of the economic evaluation for macitentan versus placebo as monotherapy in patients with WHO FC III/IV PAH**

Component	Macitentan	Placebo	Increment
Costs <sup>a</sup>	\$35,131	\$0	\$35,131
Number of first MM events per person-year*	██████	██████	-██████
<b>Incremental cost/first MM event per person-year prevented*</b>			<b>\$██████</b>

MM = morbidity or mortality; PAH = pulmonary arterial hypertension; WHO FC = World Health Organisation Functional class

<sup>a</sup> Weighted cost based on 23% private and 77% public

\* Over the duration of the trial

Source: Source: Table D.2-3, p99 of the submission; Costs of macitentan were recalculated during the evaluation.

- 6.43 The following make the interpretation of the results difficult:
- The definition of the composite primary outcome, time to first MM event, differed between the trials:
    - The components included in the composite outcome differed
    - The definition and duration of follow-up of death events differed;
  - The potential difference in the relative contribution of component MM events, of varying clinical relevance, to the composite outcome between the trials;
  - MM events subsequent to the first primary outcome event have not been compared; given the difference in the circumstances of use of the drugs (combination therapy versus monotherapy) the rate of subsequent events may differ.
- 6.44 The estimated ICER for selexipag when used as add-on therapy in patients with WHO FC III/IV PAH was approximately \$105,000 - \$200,000 per first MM event per person-year avoided, based on the proposed effective price. In comparison, the ICER for macitentan when used as monotherapy in this population was approximately \$105,000 - \$200,000 per first MM event per person-year avoided.
- 6.45 A formal cost-utility analysis was not presented in the submission. The ESC considered that the translation of first MM events prevented to life-years gained or QALYs gained may have been informative for the PBAC in comparing ICERs across drugs for the same disease.
- 6.46 The cost-effectiveness of selexipag compared to other potentially relevant active comparators, including sildenafil, iloprost and epoprostenol, when used as add-on therapy in the relevant population, is not known.

**Drug cost/patient/year: \$██████ (public), \$██████ (private)**

- 6.47 This cost was based on the proposed dispensed price per maximum quantity (DPMQ), assuming that patients receive 12.2 scripts per year.
- 6.48 The proposed DPMQ for patients on continuing treatment was \$██████ (public) and \$██████ (private). As PAH is a chronic disease, treatment is intended to be ongoing.

6.49 The submission proposed a Special Pricing Arrangement (see below).

**Estimated PBS usage & financial implications**

6.50 This submission was not considered by DUSC.

6.51 The submission used a market-share approach to estimate the extent of use and financial implications associated with the listing of selexipag, based on the estimated uptake of selexipag in patients currently accessing first-line PAH agents on the PBS. This approach was reasonable.

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

**Table 10: 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 treated					
Market share	20%	30%	40%	45%	50%
Packs <sup>a</sup>					
<b>Estimated net cost to PBS/RPBS</b>					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Proposed rebate <sup>b</sup>	-\$	-\$	-\$	-\$	-\$
<b>Cost to PBS/RPBS after rebate</b>	<b>\$</b>	<b>\$</b>	<b>\$</b>	<b>\$</b>	<b>\$</b>

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

<sup>b</sup> The submission proposes a Special Pricing Arrangement in which the sponsor would rebate \$ per prescription of selexipag (see below)

Source: Tables E.2-1 and E.2-3 pp103-4 of the submission; Excel workbook “Economic and financial analyses - selexipag - PAH” supplied in the submission”.

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

6.53 There was potential for the net cost/year for the PBS to be greater than the estimate in the submission given the potential for the uptake of selexipag to be higher than assumed in the submission, especially in the first few years of listing, when prevalent patients currently receiving non-PBS subsidised add-on therapy may switch to PBS-subsidised selexipag.

6.54 The submission’s estimates did not account for the average use and cost of selexipag during the dose titration phase in patients initiating treatment with selexipag; all patients were assumed to receive 12 packs of selexipag per year.

**Financial Management – Special Pricing Arrangement**

6.55 The sponsor proposed to rebate the Commonwealth of Australia \$ per prescription of selexipag dispensed on the PBS under a formalised Deed of Agreement. This equates to effective dispensed prices of \$ (public hospital) and \$ (private hospital).

*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 PAH. In reaching this conclusion, the PBAC considered that the magnitude of clinical benefit was unclear, and that the estimate of cost-effectiveness as presented in the submission was difficult to interpret. The PBAC considered that the ICER presented in the submission was high, especially in the context of an outcome of unclear clinical importance (MM events avoided).
- 7.2 The PBAC considered that the hearing and consumer input helped to clarify that the appropriate place in therapy for selexipag was likely to be third line – that is, after patients have tried ERAs and PDE-5 inhibitors as monotherapy and combination. This use might be as triple or dual therapy.
- 7.3 The PBAC acknowledged the difficulty in assessing the cost-effectiveness of selexipag as add-on to combination therapy in the context of combination therapy being broadly accepted as best clinical practice but not currently being subsidised under the PBS. The PBAC agreed that the submission's nomination of placebo (as add-on to combination therapy) was the appropriate comparator.
- 7.4 The PBAC considered that the clinical data were likely to be biased in favour of selexipag. In particular the PBAC were concerned about the differential censoring and treatment unblinding in the study.
- 7.5 The PBAC agreed with the ESC that the use of a composite outcome where death has the same clinical relevance as hospitalisation made the results difficult to interpret. The PBAC noted that the results for selexipag appeared to be largely driven by the hospitalisation and escalation of treatment. The relationship between these outcomes and disease progression remains unclear.
- 7.6 The PBAC agreed that treatment with selexipag was likely to be superior to placebo, but that the magnitude, and clinical relevance, of any benefit remained unclear.
- 7.7 Overall, the PBAC considered that the trial based analysis presented in the submission did not reflect life-long nature of the condition and did not give a reliable estimate of cost-effectiveness. The ICER was difficult to interpret but appeared high, particularly in the context of an outcome of uncertain clinical significance.
- 7.8 The PBAC acknowledged that the comparison with macitentan had been presented to give some context to the trial based analysis, but did not consider that this was informative given the differences between the products, including differences in the definition of outcomes reported in the studies, and recommended/proposed listings. The PBAC were also concerned about the potential difference in the relative contribution of component MM events, of varying clinical relevance, to the composite outcome between the trials.
- 7.9 The PBAC considered that the best estimate of cost-effectiveness would come from a formal cost-utility analysis. The PBAC agreed with the ESC that the translation of first MM events prevented to life-years gained or QALYs gained would have been informative for the PBAC in comparing ICERs across drugs for the same disease.
- 7.10 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 when lodging a re-submission requesting PBS listing of selexipag for patients with PAH.