

**7.07 SELEXIPAG,
Tablets, 200, 400, 600, 800, 1000, 1200, 1400, 1600
microgram,
Uptravi[®],
Janssen-Cilag Pty Ltd.**

1 Purpose of submission

- 1.1 The resubmission requested a Section 100 – Highly Specialised Drugs listing for selexipag as triple agent sequential add-on therapy with an endothelin receptor antagonist (ERA) and a phosphodiesterase-5 inhibitor (PDE-5i) for patients with World Health Organisation (WHO) Functional Class (FC) III or IV pulmonary arterial hypertension (PAH). This was the third PBAC submission for selexipag, previous submissions were considered in March 2016 and March 2017.
- 1.2 This resubmission also requested that the PBAC consider listing for selexipag dual therapy with an ERA or a PDE-5i on the basis of unmet clinical need for combination therapy with selexipag in patients who are intolerant or contraindicated to an ERA or a PDE-5i (similar to the March 2017 submission). The resubmission suggested this population is likely to be small. Although the main trial, GRIPHON, did include use of selexipag as dual therapy in combination with either an ERA or PDE-5i, it was unknown if patients in the trial also had intolerance/contraindication to either an ERA or PDE-5i. The Pre-Sub-Committee Response (PSCR) stated that there were no population specific data available from the trial to support this listing. Although the ESC agreed that this population would likely be small, the ESC noted that the submission did not present a proposed restriction or any clinical evidence for the proposed population. The ESC noted that in the PBAC Post Market Review (PMR) of PAH medicines that “The PBAC was of a mind to recommend combination therapy with a prostanoid and sildenafil (or tadalafil at a comparable price) as second line treatment for patients with WHO FC III symptoms and first line treatment for patients with WHO FC IV symptoms” (paragraph 5.40, PAH PMR, November 2019).
- 1.3 Listing for selexipag in triple combination therapy was requested on the basis of a cost utility analysis versus placebo (Table 1).

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Add-on therapy for patients with WHO FC III or IV PAH demonstrating an inadequate clinical response or deterioration whilst on stabilised doses of an ERA and a PDE-5i (i.e. sequential triple therapy).
Intervention	Selexipag. Dosing is individualised, with upward titrations from 200 mcg given bd until the maximum tolerated dose is found, or until a maximum dose of 1600 mcg bd is reached.
Comparator	Placebo. This was previously accepted by the PBAC.
Outcomes	The primary endpoint in the GRIPHON trial was time to first morbidity/mortality (MM) event defined as time to first occurrence of a CEC-confirmed MM event defined as a composite of: - death (all-causes); or - hospitalisation for PAH; or - progression of PAH resulting in need for lung transplantation or balloon atrial septostomy; or - initiation of parenteral prostanoid therapy or chronic oxygen therapy; or - other disease progression events confirmed by decrease ($\geq 15\%$) in 6MWD from baseline and need for additional PAH-specific therapy.
Clinical claim	In patients with WHO FC III or IV PAH not achieving treatment targets on dual therapy with an ERA and PDE-5i, selexipag as a sequential add-on treatment (triple therapy) has superior efficacy but inferior safety to placebo.

bd = twice daily; CEC = Critical Event Committee; ERA = endothelin receptor antagonist; FC = functional class; MM = morbidity/mortality; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type 5 inhibitor; WHO = World Health Organization; 6MWD = 6-minute walk distance

Source: Table 1.1, p13 and pp60-61 of the resubmission.

2 Background

Registration status

- 2.1 Selexipag was approved by the TGA on the 24th March 2016 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 and pulmonary arterial hypertension associated with drugs and toxins, in patients with WHO FC II, III or IV symptoms.
- 2.2 The TGA approved uses of selexipag are either as combination therapy in patients insufficiently controlled with an ERA and/or a PDE-5i, or as monotherapy in patients who are not candidates for these therapies. The proposed PBS listing for triple therapy in combination with an ERA or a PDE-5i in patients with WHO FC III and IV PAH is narrower than the TGA indication.

Previous PBAC consideration

- 2.3 The two previous PBAC considerations of selexipag for PAH were in March 2016 and March 2017. Actelion (now part of the same group of companies as Janssen-Cilag, the current sponsor) was the sponsor for both submissions.
 - In March 2016, the PBAC rejected the first submission of selexipag as add-on therapy in PAH patients who are already receiving a PBS-subsidised PAH agent (i.e. dual therapy) on the basis that the magnitude of clinical benefit was unclear (surrogate endpoint used), and cost-effectiveness estimates were difficult to interpret and appeared high on a background of uncertain clinical significance.

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- In March 2017, the PBAC rejected the second submission of selexipag for treatment of PAH for use as a triple therapy component in combination with an ERA and a PDE-5i. This decision was on the basis that the incremental cost effectiveness ratios (ICERs) presented remained difficult to interpret and were too high to support the cost-effectiveness of selexipag for the requested listing.
- 2.4 The current resubmission was made on the basis that dual combination therapy with an ERA and a PDE-5i was anticipated to be PBS listed in the near future. Dual therapy was recommended by the PBAC in consideration of the PMR of PAH medicines at its November 2019 meeting, pending acceptable price proposals from the relevant sponsors. As a result of the PMR, commencing 1 May 2020, the restriction for PBS subsidised monotherapies for PAH (ERAs: ambrisentan, bosentan and macitentan; and PDE-5i's: sildenafil and tadalafil) were extended to include patients with WHO FC II symptoms¹.
- 2.5 Table 2 summarises the key outstanding matters of concern to the PBAC and how they are addressed in the resubmission.

¹ Information for Healthcare Professionals and Patients, Pharmaceutical Benefits Scheme (PBS) – Revised PBS listings for Pulmonary Arterial Hypertension Medicines, available from <http://www.pbs.gov.au/industry/listing/participants/public-release-docs/pulm-art-hypertension/PAH-fact-sheet-monotherapy-restriction-changes-1-May-2020.pdf>, accessed 13 May 2020.

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Table 2: Summary of key matters of concern to the PBAC and how they are addressed in the resubmission

Component	Matter of concern	How the resubmission addresses it
Clinical claim and effectiveness	- The PBAC considered that treatment with selexipag was likely to be superior to placebo, but that the magnitude, and clinical relevance, of any benefit remained unclear (para 7.3, selexipag PSD, March 2017). - The use of a composite outcome where death has the same clinical relevance as hospitalisation made the results difficult to interpret (para 7.5, selexipag PSD, March 2016)	Results from a new publication (McLaughlin et al., 2018) were presented that investigated the impact of morbidity events on subsequent mortality risk using the landmark method.
Clinical claim and effectiveness in the proposed PBS population	- The ITT population did not reflect the proposed PBS reimbursed population in terms of WHO FC or PAH therapy at baseline (para 6.19, selexipag PSD, March 2017)	Post-hoc analyses of the GRIPHON trial stratified by subgroups (Coghlan et al., 2018a). Composite outcome results for patients receiving dual therapy (ERA + PDE-5i) were presented in WHO FC II and III patients.
Economic model / cost effectiveness	- ICERs appeared high and difficult to interpret in the context of unclear clinical importance of MM outcome (para 7.1, selexipag PSD, March 2016 and para 7.1 selexipag PSD, March 2017) - PBAC considered that the best estimate of cost-effectiveness would come from a formal cost-utility analysis (para 7.9, selexipag PSD, March 2016) - Trial-based analysis did not reflect the life-long nature of PAH (para 7.7, selexipag PSD, March 2016)	A new a cost utility analysis was presented based on results of GRIPHON trial subgroup with WHO FC III PAH on dual therapy with an ERA and a PDE-5i at baseline. Results presented as costs per QALY gained in the model.

ERA = endothelin receptor antagonist; FC = functional class; ICER = incremental cost effectiveness ratio; ITT = intention-to-treat; MM = morbidity/mortality; PAH = pulmonary arterial hypertension; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PDE-5i = phosphodiesterase type 5 inhibitor; PSD = Public Summary Document; QALY = quality adjusted life year; WHO = World Health Organisation

Source: compiled during the evaluation based on information presented in Table 1.6, pp40-44 of the resubmission and the past PBAC minutes

3 Requested listing

3.1 The requested listing is presented below.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
<u>Initial treatment:</u> SELEXIPAG Tablets 200mcg	140	2	\$ [redacted] (public) \$ [redacted] (private)	UPTRAVI® Janssen Cilag Pty Ltd
<u>Initial treatment:</u> SELEXIPAG Tablets 800mcg	60	3	<u>Published:</u> \$3,450.00 (public) \$3,497.39 (private) <u>Effective:</u> \$ [redacted] (public) \$ [redacted] (private)	UPTRAVI® Janssen Cilag Pty Ltd
<u>Continuing treatment</u> SELEXIPAG Tablets 200, 400, 600, 800, 1000, 1200, 1400, 1600 mcg	140	2	<u>Published</u> \$3,450.00 (public) \$3,497.39 (private) <u>Effective:</u> \$ [redacted] (public) \$ [redacted] (private)	UPTRAVI® Janssen Cilag Pty Ltd

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Category/Program:	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS indication:	Pulmonary arterial hypertension
Treatment phase:	Initial and maintenance
Restriction:	Initial treatment: Authority Required - In Writing Continuing treatment: Authority Required – Telephone, Electronic
Treatment criteria:	Initial treatment: Dose titration must be completed within a maximum of 12 weeks Continuing treatment: Continuing
Clinical criteria:	<p>Initial treatment: Patients must have WHO Functional Class III PAH or WHO Functional Class IV PAH AND Patient must have received prior dual therapy with a phosphodiesterase-5 inhibitor (PDE-5i) agent and an endothelin receptor antagonist (ERA) for pulmonary arterial hypertension (PAH) AND The treatment must be in combination with a phosphodiesterase-5 inhibitor (PDE-5i) agent and an endothelin receptor antagonist (ERA) for this condition.</p> <p>Continuing treatment: Patients must have received this agent as their most recent course of PBS-subsidised treatment for this condition OR Patient must have received non-PBS subsidised therapy with this agent as part of triple therapy with a phosphodiesterase-5 inhibitor (PDE-5i) agent and an endothelin receptor antagonist (ERA), prior to [LISTING DATE] for this condition and must currently have, or have had WHO Functional Class III PAH or WHO Functional Class IV PAH AND The treatment must be in combination with a phosphodiesterase-5 inhibitor (PDE-5i) agent and an endothelin receptor antagonist (ERA) for this condition AND Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition.</p>
Population criteria:	<p>PAH (WHO Group 1 pulmonary hypertension) currently includes the following subtypes:</p> <ul style="list-style-type: none"> • Idiopathic PAH • Heritable PAH <ul style="list-style-type: none"> o BMPR2 mutation o ALK-1, ENG, SMAD9, CAV1, KCNK3 mutations o Other mutations • Drugs and toxins induced PAH • PAH associated with: <ul style="list-style-type: none"> o Connective tissue disease o Human immunodeficiency virus (HIV) infection o Portal hypertension o Congenital heart disease <p>o Schistosomiasis</p>
Prescriber criteria:	<p>The maximum quantity authorised will be limited to provide sufficient supply for 1 month of treatment, based on the dosage recommendations in the TGA-approved Product Information. A maximum of 5 repeats will be authorised. For the purposes of PBS subsidy, dual combination therapy refers to the combined use of one agent from each of the following classes: (i) Endothelin receptor antagonists (ERAs): ambrisentan, and macitentan (ii) Phosphodiesterase-5 inhibitors (PDE-5i): sildenafil citrate, and tadalafil. 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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Administrative Advice	Note Special Pricing Arrangements apply
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Note: this is a summarised presentation of the requested restrictions for initial and continuing therapy.

- 3.2 The resubmission proposed a Special Pricing Arrangement (SPA) for all maintenance packs of selexipag as well as the 800 mcg strength initiation pack. A flat pricing structure was proposed for these packs. The effective prices proposed in the resubmission were the same as those in the March 2017 resubmission. However, contrary to the March 2017 resubmission, the 200 mcg initiation pack was excluded from the SPA (resulting in an additional \$ [REDACTED] per initiation pack prescription). Another difference from the March 2017 resubmission was the removal of the offer to rebate [REDACTED]% of the cost of sildenafil when used as add-on to Actelion-sponsored ERA products (i.e., TRACLEER® branded bosentan and OPSUMIT® branded macitentan) (paragraph 6.1, selexipag Public Summary Document (PSD), March 2017); the dispensed price for maximum quantity (DPMQ) (S100 HSD Public) of sildenafil as of 1 April 2020 was \$254.31 for a 30-day supply. Given these changes, the overall requested price for selexipag in this resubmission was higher than that requested in the March 2017 resubmission. In the pre-PBAC response, a reduced price for selexipag was proposed of \$ [REDACTED] per pack (i.e. for both the titration and continuing packs). This represented a [REDACTED]% reduction for the 200 mcg and 800 mcg initiation packs, a [REDACTED]% reduction for the maintenance packs and a [REDACTED]% reduction overall.
- 3.3 The requested quantities were intended to provide up to 12 weeks of treatment for initial therapy and 6 months of treatment for continuation therapy (taking into account individualised dosing). In GRIPHON, the main trial supporting the resubmission, initiating patients used an average of 1.65 packs of the 200 mcg tablets and 0.65 of the 800 mcg tablets.
- 3.4 The proposed PBS restriction is narrower than the TGA approved indication. The requested restrictions limit use to triple therapy for patients with WHO FC III and IV PAH. The ESC and PBAC considered that if selexipag is listed on the PBS as requested, leakage of use to patients with WHO FC II disease would be unlikely to occur.
- 3.5 For the purposes of PBS subsidy, the resubmission defined dual combination therapy as use of one agent from each of the following classes: (i) ERA: ambrisentan, and macitentan and (ii) PDE-5i: sildenafil citrate, and tadalafil. Notably, bosentan was removed from the ERA list. The resubmission stated the reasons behind this were:
- that bosentan is not TGA registered for dual therapy. However, sildenafil also does not have a TGA indication for combined therapy;
 - there are clinically relevant drug-drug interactions between bosentan and sildenafil/tadalafil resulting in changed pharmacokinetics of the PDE-5i and bosentan (when given with sildenafil); and
 - a demonstrated lack of a clinically significant benefit in clinical trial (the submission referenced the COMPASS-2 trial where the results showed no additional benefit for bosentan and sildenafil combination therapy over sildenafil monotherapy).

- 3.6 In November 2018 the PBAC, when considering the PMR of the PAH medicines, stated that a recommendation for dual combination therapy should be for a medicine class, instead of individual medicines (paragraph 5.4.8, PAH PMR minutes, November 2018). However, in November 2019, noting the uncertain clinical evidence to support the equi-effectiveness of bosentan plus PDE-5i combinations compared to other ERA plus PDE-5i combinations, current clinical guidelines and clinician concerns over increased hepatotoxicity, the PBAC agreed that the basis for benchmarking the price of all PBS ERA plus PDE-5i combinations to that of bosentan and sildenafil was not fully justified (paragraph 5.28, PAH PMR minutes, November 2019). In November 2019 the PBAC also considered that clinicians had adequately managed potential drug-drug interactions and safety concerns of bosentan plus PDE-5i combination use. Registry data collected by the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ) indicated that nearly 20% of patients on dual combination therapy used the bosentan + sildenafil combination, and 25% of patients used triple therapy consisting of bosentan, sildenafil and epoprostenol (paragraph 5.26, PAH PMR minutes, November 2019). Prohibiting dual therapy with bosentan would likely result in any new patients initiating monotherapy or dual therapy with an ERA to not initiate with bosentan to avoid the need to switch drugs later to qualify for triple therapy. In addition, patients otherwise stabilised on bosentan will be required to switch to another ERA to qualify for selexipag triple therapy. The modelled economic evaluation assumed that 16% of the ERA use in combination with selexipag will be with bosentan. The PSCR stated that PBS data from the last 12 months demonstrated that bosentan comprised 16.1% of ERA prescriptions, and its volume has been steadily declining since 2010. The PBAC reiterated its view from the November 2019 PMR of PAH medicines and considered that the potential drug interaction and safety concerns of the bosentan + PDE-5i combination were well understood and managed by clinicians. The PBAC considered that the proposed selexipag restriction need not be exclusive of bosentan.
- 3.7 Unlike the March 2017 request, the resubmission removed the criteria of inadequate response to dual therapy as a prerequisite for initiating selexipag. The ESC considered that progression of disease to WHO FC III represented inadequate response to dual therapy. The PBAC considered that it was not necessary to indicate a minimum duration of time on dual therapy before progressing to triple therapy with selexipag. Rather individual circumstances and adequacy of response to dual therapy as assessed by the patient and PAH physicians would better determine the timing of initiation of selexipag. The PBAC considered that progression to triple therapy should only be instituted when PAH physicians felt that there had been an adequate time to assess response to dual therapy and that, despite this, the patient remained in WHO FC III/IV.
- 3.8 For continuing maintenance therapy the resubmission proposed a new criterion: “Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition”. In the March 2017 resubmission, a continuation criterion was “Patient must have demonstrated a response within 12

weeks of initiating treatment with this drug (i.e. following titration phase)". The resubmission argued that the new criterion was akin to criterion for disease progression used in oncology treatments. The resubmission suggested the following definitions of disease progression from the GRIPHON trial including:

- Hospitalisation;
- disease progression (confirmed by $\geq 15\%$ decrease in 6-Minute Walk Distance (6MWD) from baseline plus worsening of WHO FC or need for additional PAH-specific therapy);
- initiation of parenteral prostanoid therapy or long-term oxygen therapy for worsening of PAH; and
- need for lung transplantation or balloon atrial septostomy for worsening of PAH.

3.9 Patients in GRIPHON were required to discontinue treatment with selexipag but could continue their ERA and PDE-5i upon experiencing any of the above outcomes. The ESC considered that this was reasonable.

3.10 Despite requesting the PBAC to consider an exception for selexipag as dual therapy in patients who are intolerant or contraindicated to an ERA or PDE-5i, the resubmission did not propose words for an additional eligibility clause to permit this.

3.11 Similar to other PBS listed therapies for PAH, the restriction does not specifically preclude use in children; however, the TGA approved Product Information for selexipag cautions against use in children (< 18 years of age) due to a lack of efficacy and safety data in this population.

3.12 The Highly Specialised Drugs (HSD) Program is for drugs that are highly specialised, making administration outside an institutional environment problematic. The resubmission requested a Section 100 HSD Program listing for selexipag as, currently, the PBS listed ERAs and PDE-5i have Section 100 HSD Program listings. The administration of selexipag outside an institution environment was considered by the PBAC to be non-problematic, as it is an orally administered drug that is unlikely to have immediate, life-threatening administration sequelae for which an institutional environment equipped with resuscitation equipment and expertise to handle an acute medical emergency, would be needed. Therefore, listing selexipag under special circumstances through the Section 100 HSD Program, was not considered appropriate.

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

4 Population and disease

4.1 PAH is a rare, intractable and progressive disease characterised by high pressure in the pulmonary arteries, which can lead to right heart failure and premature death. Patients with PAH experience a high co-morbidity burden and negative impacts on quality of life. The goal of PAH therapy is to achieve a low-risk (I or II) WHO FC status. WHO FC I status is defined as no limitation of usual physical activity and where ordinary physical activity does not cause increased dyspnoea, fatigue, chest pain, or

presyncope. WHO FC II status is defined as mild limitation of physical activity where there is no discomfort at rest, but normal physical activity causes increased dyspnoea, fatigue, chest pain, or presyncope.

- 4.2 The resubmission argued that, despite available treatments, there remains an unmet clinical need for patients who experience clinical worsening or disease progression while stabilised on dual therapy with an ERA and a PDE-5i. The most widely used treatment strategy for PAH is sequential combination therapy using agents of different mechanisms. Selexipag is a selective, I-prostanoid receptor agonist; it is structurally and pharmacologically distinct from prostacyclin analogues (such as iloprost or epoprostenol, which are also PBS listed for PAH). It can be used in combination with a PDE-5i that targets the nitric oxide pathway and an ERA that targets the endothelin pathway; enabling synergistic effects covering each of the three pathways implicated in the molecular pathophysiology of PAH.

5 Comparator

- 5.1 Placebo was nominated as the main comparator, consistent with the March 2016 and 2017 submissions. The PBAC previously agreed that placebo (as add-on to an ERA or PDE-5i, or both) was an appropriate comparator (paragraph 7.3, selexipag PSD, March 2016).
- 5.2 The resubmission also reasonably argued that intravenous (IV) epoprostenol would not be a main comparator as selexipag would displace, rather than replace its use. Although not discussed in the resubmission, similar arguments would also likely apply to inhaled iloprost (which is administered six to nine times per day).

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 described the importance of additional treatment options for late-stage PAH and highlighted the ongoing high mortality rate in this disease and the issues with current treatments which act on the prostacyclin pathway, including limited evidence of long-term benefit with inhaled iloprost and the severe quality of life decrements associated with the use of IV epoprostenol. The clinician also highlighted the additional health system costs and patient burden associated with IV epoprostenol, particularly in terms of long hospitalisation at treatment initiation. The PBAC considered that the presentation was informative as it provided a clinical perspective on treating PAH.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (113), health care professionals (26) and organisations (3) via the Consumer Comments facility on the

PBS website. The majority of the consumer comments, as well as patient advocates from the Pulmonary Hypertension Network Australia, the Lung Foundation Australia and PAH Association of Australia, described living with PAH and the reduced ability to undertake daily activities. The comments also described treatment with IV epoprostenol and the risks associated with the continuous IV infusion, including pump failure and infections. The health professionals and patients highlighted the efficacy of selexipag and quality of life benefits patients would experience if IV epoprostenol could be delayed or avoided through the PBS listing of selexipag.

Clinical trials

- 6.3 As per the March 2016 and March 2017 submissions, the resubmission was based on one head-to-head trial (GRIPHON, N=1,156) which compared selexipag to placebo in a broad population of PAH patients (WHO FC I to IV) and included treatment naïve and patients receiving single or dual alternative PAH therapies. In addition, three new GRIPHON publications (two full publications: McLaughlin et al 2018 and Coghlan et al 2018a; and one conference abstract: Coghlan et al 2018b) were presented, which provided new information:
- McLaughlin et al 2018, presented a post hoc analysis of the GRIPHON trial (plus results from SERAPHIN trial of macitentan versus placebo) and the impact of morbidity events on the risk of subsequent mortality at 3, 6 and 12-month landmark time points;
 - Coghlan et al 2018a, was a subgroup analysis of patients with WHO FC III severity and receiving double combination therapy at baseline. This was used by the resubmission as proxy for the proposed PBS population; and
 - Coghlan et al 2018b reported survival and adverse events data up to 5 years from the open label extension (OLE) of the GRIPHON trial. At the data cut of 20 December 2017, 180 patients had received selexipag for at least 5 years.
- 6.4 The details of the GRIPHON trial and associated reports presented in the resubmission are provided in Table 3.

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Table 3: GRIPHON trial and associated reports presented in the submission

	Protocol title/ Publication title	Publication citation
GRIPHON	GRIPHON Clinical study report AC-065A302: Prostacyclin (PGI ₂) 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, Chin KM, et al. Selexipag for the Treatment of Pulmonary Arterial Hypertension.	March 2014 (data cut-off) NEJM 2015; 373(26):2522–2533
GRIPHON sub-group analyses, post-hoc analyses and sub-studies	Coghlan JG, Channick R, Chin K, et al. Targeting the prostacyclin pathway with selexipag in patients with pulmonary arterial hypertension receiving double combination therapy: insights from the randomized controlled GRIPHON study. McLaughlin VV, Hoepfer MM, Channick RN, et al. Pulmonary arterial hypertension-related morbidity is prognostic for mortality.	American Journal of Cardiovascular Drugs. 2018 Feb 1;18(1):37-47. Journal of the American College of Cardiology. 2018 Feb 12;71(7):752-63.
GRIPHON open label extension (abstract only)	Coghlan JG, Galiè N, Gaine S, et al. Long-term survival and safety with selexipag in patients with pulmonary arterial hypertension: results from the GRIPHON study and its open-label extension. Thorax 2018;73:A76-A77	Thorax 2018;73:A76-A77

Source: Table 1, 5.11 selexipag PSD, March 2016 PBAC meeting; Table 2.4, p68-69 of the submission.

6.5 The key features of the GRIPHON randomised trials and the three new associated reports are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Selexipag versus placebo						
GRIPHON	1156	R, DB 6 mths	Low	Broad population of PAH patients (WHO FC I to IV): Treatment naive, or background single or dual therapy	¹⁰ time to first CEC-confirmed MM event	Yes, for time to mortality event (assumed same for selexipag and placebo).
McLaughlin et al 2018	1127*	Post hoc analysis of the GRIPHON trial (plus results from SERAPHIN trial of macitentan versus placebo) to look at the impact of morbidity events on the risk of subsequent mortality at 3, 6- and 12-months landmark time points.				No
Coghlan 2018a	255	Subgroup analysis of patients receiving dual background therapy with an ERA and a PDE-5i at baseline and had WHO FC III disease				Yes, subgroup results used for time to morbidity event.
Coghlan 2018b	953#	OL extension of the GRIPHON trial. Reported survival and AEs up to 5 years follow up (data cut off 20 Dec 2017); 180 patients had been receiving selexipag for at least 5 years.				No

¹⁰ = primary outcome, AE = adverse event; CEC = Critical Event Committee; DB = double blind; ERA = endothelin receptor antagonist; FC = functional class; MM = morbidity/mortality; OL = open label; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type 5 inhibitor; R = randomised; WHO = World Health Organisation

* Patients from GRIPHON evaluated at land mark times, n=1127 at 3 months, n=1089 at 6 months and n= 964 at 12 months.

Comprising 574 patients who received selexipag in the DB phase and 379 who switched from placebo to selexipag in the OL extension

Source: compiled during the evaluation

6.6 The risk of bias in the GRIPHON trial was considered overall to be low. However, as raised in previous commentaries, the occurrence of typical prostacyclin receptor agonist adverse events, especially during dose titration, and the resulting difference in the distribution of the maximum tolerated dose of medication achieved by patients may have led to a degree of unblinding of investigators and patients.

Comparative effectiveness

Primary endpoint: time to first CEC-confirmed MM event (up to 7 days after treatment end), ITT and subgroup results

6.7 The primary trial outcome from GRIPHON of time to first Critical Event Committee (CEC) confirmed morbidity/mortality (MM) event (up to 7 days after treatment end) was previously presented in the March 2016 submission. This resubmission presented the intention to treat (ITT) results plus additional primary outcome results stratified by subgroups receiving background dual therapy (an ERA plus a PDE-5i) from Coghlan et al 2018a. Table 5 summarises the results of the ITT population and subgroups. Blue shading represents results previously seen by the PBAC.

Table 5: Results of primary outcome time to first CEC-confirmed MM event (up to 7 days after treatment end) in the GRIPHON trial (ITT and subgroups as defined by Coghlan et al 2018a)

GRIPHON ITT and subgroups	Selexipag	PBO	HR (99% CI)*
GRIPHON ITT population			
Median duration of follow-up, weeks (IQR)	70.7 (32.0, 117.1)	63.7 (28.6, 107.1)	-
Primary outcome first CEC-confirmed MM event, n/N (%)	140/574 (24.3%)	212/582 (36.4%)	0.61 (0.46, 0.81)[^] p<0.0001
Subgroup analysis patients receiving background dual therapy of an ERA + a PDE-5i (Coghlan et al 2018a)			HR (95% CI)
All patients receiving background dual therapy	47/179 (26%)	80/197 (41%)	0.63 (0.44, 0.90)[§]
WHO FC II patients receiving background dual therapy	6/55 (11%)	18/60 (30%)	0.36 (0.14, 0.91)[§]
WHO FC III patients receiving background dual therapy	41/122 (34%)	59/133 (44%)	0.74 (0.50, 1.10) [§]

Blue shading indicates results previously seen by the PBAC; **Bold** typography indicates statistically significant results.

CEC = Critical Event Committee; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; HR = hazard ratio; IQR = interquartile range; ITT = intention to treat; MM = morbidity/mortality; PBO = placebo; PDE-5i = phosphodiesterase type 5 inhibitor; WHO = World Health Organisation

* one sided unstratified log-rank

[^] result from the GRIPHON trial Clinical Study Report (Table 15-48), it was noted that the published report by Sitbon et al 2015 had reported slightly different HR (99% CI) of 0.60 (0.46, 0.78) with a total of 155 and 242 primary outcomes events in selexipag and placebo groups, respectively. Inclusion or exclusion of events occurring prior to 16 August 2011 (n=45) accounts for the discrepancy in event rates which occurred as a result of a Global Protocol Amendment. Both sets of results were presented in the resubmission.

[§] Analyses were unadjusted for 6-Minute-Walk-Distance. Adjusted results (for 6MWD): HR = 0.37; 95% CI: 0.15, 0.95 in patients with WHO FC II symptoms (on background dual therapy) and HR = 0.67; 95% CI: 0.45, 1.01 in patients with WHO FC III symptoms (on background dual therapy).

Source: GRIPHON trial Clinical Study Report pp199; Sitbon et al (2015) Table 2, pp2529; Coghlan et al (2018a): in-text results pp40 and Figure 2, pp42.

6.8 For the ITT population, comprised of a broad population of patients with WHO FC I-IV disease (although 98.3% of the population had WHO II or III PAH) and taking a range of concomitant therapies (including treatment naïve, monotherapy with an ERA or PDE-5i or dual therapy with both agents), the GRIPHON trial found selexipag treatment

to be associated with a 39% risk reduction for the primary endpoint of first CEC-confirmed MM event (HR = 0.61, 99% CI: 0.46, 0.81) versus placebo-treated patients.

- 6.9 The subgroup analysis for all patients receiving dual ERA plus PDE-5i therapy at baseline (n=376) demonstrated a statistically significant and similar risk reduction for the primary endpoint (HR = 0.63, 95% CI: 0.44, 0.90) compared to the ITT population. The result for the WHO FC II subgroup receiving dual therapy (n=115) also demonstrated significantly reduced risk of the primary endpoint in selexipag-treated patients versus placebo, although the confidence interval was wider (HR = 0.36, 95% CI: 0.14, 0.91). However, for the WHO FC III subgroup receiving dual therapy, no significant difference was observed between selexipag and placebo groups (HR = 0.74, 95% CI, 0.50, 1.10). In addition, an adjusted Cox regression subgroup analysis of patients with WHO FC III and receiving background dual therapy demonstrated [REDACTED], which was consistent with the analysis presented by Coghlan et al (2018a) above.
- 6.10 Coghlan et al 2018a stated “Our data indicate that the relative reduction in the risk of morbidity/mortality events with selexipag versus placebo may be more pronounced in patients with WHO FC II symptoms, and a similar observation has been reported previously in PAH. While these data raise the possibility that patients with less progressive disease respond better to therapy, caution is required to avoid over-interpretation of these post-hoc subgroup analyses. The number of morbidity/mortality events in the WHO FC II subgroup analysis was low (6% of all events in the study), the interaction p-value of 0.1436 indicates consistency in the results, irrespective of WHO FC, and there was also no difference in the treatment response between patients with WHO FC II and III symptoms in the GRIPHON population as a whole.”
- 6.11 The PSCR and pre-PBAC response stated that the subgroup analyses were not powered to demonstrate treatment effects, thus the lack of statistical significance was the result of a Type II error.
- 6.12 No data were available from the GRIPHON trial to determine the efficacy of sequential triple therapy of selexipag added to background dual therapy of an ERA and a PDE-5i in patients with WHO FC IV disease, due to insufficient sample size (n=6). The resubmission requested listing in this patient population on a high clinical need basis and argued that there is no biological rationale to consider that the relative treatment benefit from triple therapy with selexipag will be significantly different in WHO IV patients. The ESC agreed with the clinical need, but considered that this statement was not adequately supported, particularly given the evidence illustrating better efficacy for WHO FC II versus III patients. The PBAC considered that the data from the relatively few WHO FC IV patients in the GRIPHON trial should have been included in the submissions subgroup analyses. The pre-PBAC response stated that, although the sponsor considered that WHO FC was not a treatment effect modifier, there was uncertainty in the magnitude of benefit of selexipag in WHO FC IV patients.

Type of first CEC-confirmed MM events in the primary composite endpoint (GRIPHON ITT and subgroups from Coghlan et al 2018a)

6.13 Table 6 summarises the type of first CEC-confirmed MM event in the primary composite endpoint for the GRIPHON ITT population and subgroups identified in Coghlan et al 2018a. Results for the subgroup of patients with WHO FC III PAH and receiving background dual combination therapy (highlighted green) are used in the modelled economic evaluation to represent the proposed PBS population.

Table 6: Type of first CEC-confirmed MM events in the primary composite endpoint# for the GRIPHON ITT population and subgroups identified in Coghlan et al 2018a

GRIPHON trial and subgroups	ITT*		Background dual therapy		Background dual therapy + WHO FC II		Background dual therapy + WHO FC III	
	Selexipag N=574	Placebo N=582	Selexipag N=179	Placebo N=197	Selexipag N=55	Placebo N=60	Selexipag N=122	Placebo N=133
Component outcomes of primary composite endpoint, n/N (%)								
All events	155 (27%)	242 (41.6%)	47 (26.3%)	80 (40.6%)	6 (10.9%)	18 (30%)	41 (33.6%)	59 (44.4%)
Death	28 (4.9%)	18 (3.1%)	4 (2.2%)	3 (1.5%)	0	1 (1.7%)	4 (3.3%)	2 (1.5%)
Hospitalisation for PAH worsening	78 (13.6%)	109 (18.7%)	27 (15.1%)	43 (21.8%)	3 (5.5%)	8 (13.3%)	24 (19.7%)	33 (24.8%)
Parenteral prostanoid or chronic oxygen therapy	10 (1.7%)	13 (2.2%)	5 (2.8%)	10 (5.1%)	2 (3.6%)	3 (5.0%)	3 (2.5%)	7 (5.3%)
PAH worsening resulting in need for lung transplantation or balloon atrial septostomy	1 (0.2%)	2 (0.3%)	0	2 (1.0%)	0	1 (1.7%)	0	1 (0.75%)
Disease progression [^]	38 (6.6%)	100 (17.2%)	11 (6.1%)	22 (11.2%)	1 (1.8%)	5 (8.3%)	10 (8.2%)	16 (12.0%)

Blue shading indicates results previously seen by the PBAC. Green shading indicates results used in the modelled economic evaluation. CEC = Critical Event Committee; FC = functional class; ITT = intention to treat population including all randomised patients (note the resubmission referred to this group as the Full Analysis Set); MM = morbidity/mortality; PAH = pulmonary arterial hypertension; WHO = World Health Organization; 6MWD = 6-minute walk distance

Rates for component outcomes reflect first events only as subsequent events were not accounted for (patients were right censored)

[^] Disease progression needs to be confirmed by ≥ 15% decrease in 6MWD from baseline plus: Worsening of WHO FC (for patients in WHO FC II-III at baseline); or need for additional PAH-specific therapy (for patients in WHO FC III-IV at baseline).

* All events for the ITT population are based on table 15-48 of the CSR which included CEC-confirmed events dated up until 16 August 2011, which is what was also presented in the publication by Sitbon et al (2015). These event rates differ from Table 5 which did not include events occurring prior to 16 August 2011 (n=45).

Source: Primary endpoints: Table 2.20, pp104 of the resubmission, Table 15-48 of GRIPHON CSR, Post-hoc subgroups analyses: Coghlan et al (2018a), pp42.

6.14 The ITT results for the composite MM outcome were largely driven by hospitalisation and disease progression. A similar pattern with respect to the component outcomes of the primary composite outcome was observed for the subgroups of patients who were receiving background dual therapy at baseline.

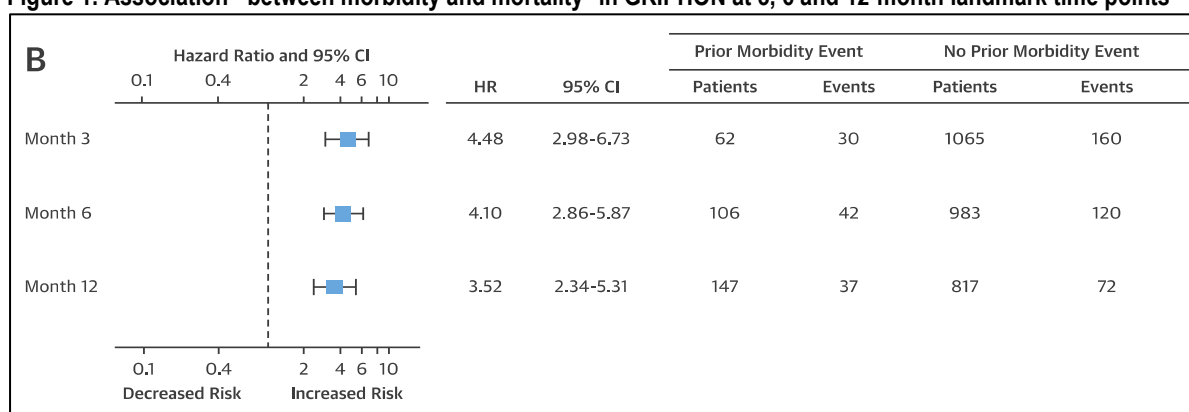
6.15 In relation to the higher number of deaths reported in the selexipag treatment arm (28) versus placebo (18), the resubmission argued that informative censoring in the trial due to more morbidity events in the placebo arm had biased the results against selexipag. The ESC considered that this was plausible. Overall, the mortality results between selexipag (4.9%) and placebo (3.1%) were similar. The ESC noted that the modelled economic evaluation appropriately assumed similar survival for selexipag

and placebo based on survival in the selexipag arm of the GRIPHON trial (see paragraph 6.46).

Landmark analysis investigating prognostic relevance of PAH-morbidity for mortality (McLaughlin et al 2018)

6.16 Results of landmark analyses investigating prognostic relevance of PAH-morbidity for mortality by McLaughlin et al 2018 is presented in Figure 1. A comparison is made for death rates in those with prior morbidity events and those without.

Figure 1. Association[^] between morbidity and mortality* in GRIPHON at 3, 6 and 12-month landmark time points



CI = confidence interval; FC = functional class; HR = hazard ratio; WHO = World Health Organization; 6MWD = 6-minute walk distance
[^] Cox model also included baseline characteristics (i.e. WHO FC and 6MWD) to take into account potential differences between patients with and without a prior morbidity event.

* Death occurred between the landmark time point and end of study period

Source: Figure 2B, p759 of McLaughlin et al., 2018, Figure 2.16, p111 of the resubmission.

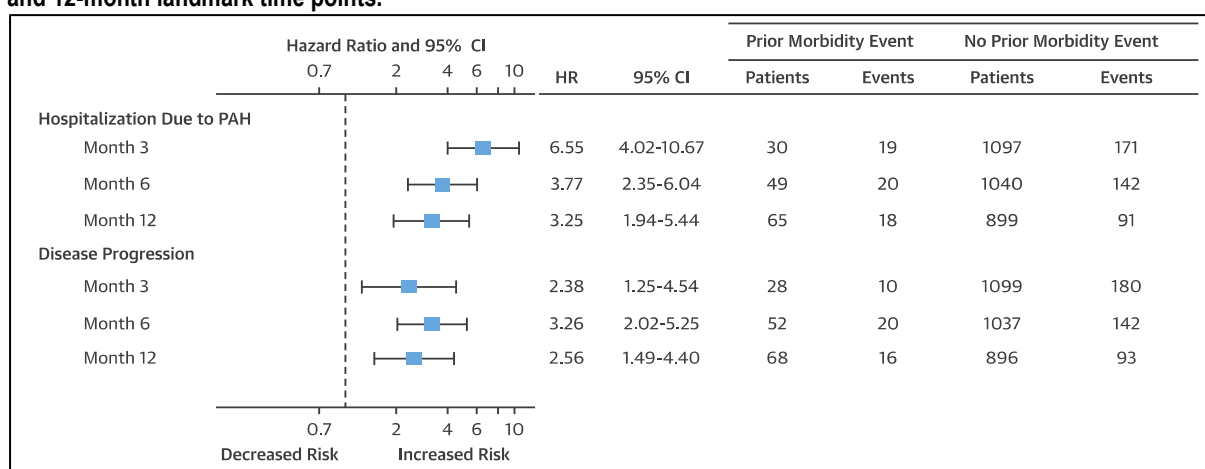
6.17 The number of GRIPHON trial patients available for survival follow-up at the 3, 6, and 12 months landmark time points were 1,127, 1,089, and 964, respectively. Differences in baseline characteristics were evident between the prior morbidity and no-morbidity groups at the landmark time points, including: 1) patients who experienced a morbidity event tended to be more impaired, with higher WHO FC status and shorter 6MWD, compared with those who did not, 2) the proportion of incident patients (enrolled ≤ 6 months after diagnosis) was greater among those who experienced a morbidity event before the 3-month landmark time point compared with those that did not (the difference dissipated at the later time points). However, the proportion of patients receiving PAH treatment at baseline did not vary greatly between those who did and those who did not experience a morbidity event.

6.18 On the basis of the 3-month and 6-month landmark time points, there was over a four-fold increased risk of death if a patient experienced a morbidity endpoint in the composite MM outcome, regardless of treatment received. The hazard ratio for risk of death for the morbidity event group was 4.48 (95% CI: 2.98, 6.73) at the 3-month landmark time point, and 4.10 (95% CI: 2.86, 5.87) at the 6-month landmark time point. Analyses based on the 12-month landmark time point also demonstrated an increased risk of death if patients experienced a morbidity endpoint (HR = 3.52, 95% CI: 2.35, 5.31). The landmark analyses suggested that morbidity, as captured in the

primary endpoint events of the GRIPHON trial, is associated with increased mortality. Caution when interpreting the results should be applied as the publication noted that patients who experienced a morbidity event tended to be more impaired, with a higher WHO FC status and shorter 6MWD, compared with those who did not experience morbidity events. In addition, the 95% confidence intervals appear wide, which reflect some overall uncertainty in results.

- 6.19 The association of individual morbidity components with the risk of death was also evaluated and demonstrated that hospitalisation due to worsening PAH and disease progression was associated with statistically significantly higher subsequent death risk at all landmark time points (Figure 2).

Figure 2. Association of hospitalisation due to PAH worsening and disease progression with mortality risk at 3-, 6- and 12-month landmark time points.



CI = confidence interval; HR = hazard ratio; PAH = pulmonary arterial hypertension
 Source: Figure 3, p760 of McLaughlin et al., 2018, Figure 2.17, p112 of the resubmission.

- 6.20 McLaughlin et al 2018 noted some nuances that should be considered when interpreting the landmark analysis results. Firstly, very few patients were excluded from follow-up at the 3-month landmark (3%), which may have led to a more representative study population at month 3, particularly when compared to latter landmark time points (6% and 17% of patients were excluded at 6 and 12-month time points, respectively). Secondly, more pronounced differences in baseline differences were apparent between patients with prior morbidity events compared to those without at the 3-month compared to the 12-month landmark time point. The study authors considered that this may have resulted in the smaller hazard ratios for later landmark time points.
- 6.21 Sensitivity analyses were undertaken by McLaughlin et al (2018) which adjusted for baseline differences in WHO FC and 6MWD (the characteristics that differed most between groups) for all associations between morbidity and mortality endpoints. The results were consistent with the primary analyses, albeit of smaller magnitudes.

Long-term efficacy data from Coghlan et al 2018b

- 6.22 Long-term survival and safety data from the GRIPHON trial and its extension study have been published since the March 2017 resubmission (Coghlan et al 2018b, Galiè et al 2018). All patients who received selexipag in the GRIPHON trial and/or the OLE were included.
- 6.23 Patients were followed for adverse events and survival from selexipag initiation until the end of treatment (up to 30 days after selexipag discontinuation for survival), or until the cut-off date (20 December 2017). At the cut-off date, 953 patients had received selexipag during the double blind trial and/or the OLE. Of the 574 patients randomised to selexipag, 330 entered the OLE and continued to receive selexipag (of these, 67 had experienced a morbidity event). A further 379 patients switched from placebo to selexipag in the OLE (160 of whom had experienced a morbidity event).
- 6.24 The median (Q1, Q3) exposure to selexipag was 135.57 weeks (48.57, 228.14) (equivalent to 2561 patient-years), and 180 patients received selexipag for at least five years. Survival estimates at 1, 2, 3 and 5 years were 92.1%, 86.4%, 80.8% and 72.9%, respectively.

Comparative harms

- 6.25 Consistent with previous submissions, the resubmission described selexipag as inferior in comparative safety compared to placebo. The PBAC have previously considered selexipag to be inferior to placebo in terms of comparative safety (paragraph 7.4, selexipag PSD, March 2017).
- 6.26 Overall, the majority of patients experienced an adverse event (98.3% selexipag, 96.9% placebo). The most frequently reported adverse events were prostacyclin associated events which occurred more frequently in the selexipag group compared to placebo. Patients receiving placebo were significantly more likely to experience worsening of PAH during the treatment period (RR = 0.66, 95% CI: 0.51, 0.84). A similar proportion of patients in trial arms experienced serious adverse events including PAH worsening (3.3% selexipag, 2.8% placebo) and right ventricular failure (1.2% selexipag, 1.0% placebo) up until end of treatment + 7 days with a subsequent fatal outcome. Events leading to study treatment discontinuation were reported in 31.7% of selexipag patients versus 37.1% for placebo patients. Adverse event rates were not adjusted for treatment duration, which introduced a likely bias in favour of placebo (median treatment duration: 70.7 weeks for selexipag; 63.7 weeks for placebo).
- 6.27 As individual maintenance doses of the study drugs were determined by up-titrating patients to the point at which the patient experienced adverse events and then back-titrating one dosing level, a greater difference in prostacyclin like adverse events were reported in titration compared to the maintenance phase of the trial.
- 6.28 Of the 218 patients enrolled in the OLE period who received selexipag, 209 (96%) experienced at least one adverse event. Prostacyclin-associated events were most prevalent. In the long-term safety and tolerability analysis, the proportion of patients

with at least one adverse event or serious adverse event was 99.4% and 56.7%, respectively. The most frequently reported adverse events (headache 67.4%, disease progression 44.5% and diarrhoea 44.3%), were related to underlying disease and/or known prostacyclin-related effects. After adjusting for exposure, the incidence per patient year for these adverse events was 0.42, 0.28 and 0.25, respectively. Overall, no specific or new safety issues were identified for selexipag.

Benefits/harms

6.29 A summary of the comparative benefits and harms for selexipag versus placebo is presented in Table 7.

Table 7: Summary of comparative benefits and harms for selexipag and comparator placebo

Benefits						
GRIPHON ITT population: Time to first CEC confirmed MM event (up to 7 days after treatment end)						
Event	Selexipag	Placebo	Absolute Difference	HR (95% CI)		
Primary outcome first CEC-confirmed MM event, n/N (%)	140/574 (24.4%)	212/582 (36.4%)	-	0.61 (0.46, 0.81) p < 0.001		
Median follow up, weeks (IQR)	70.7 (32.0, 117.1)	63.7 (28.6, 107.1)	-			
% with no event at 6 months (95% CI)	93.0% (90.5, 94.9)	85.8% (82.5, 88.5)	7.2% (NR)			
Subgroup analysis of WHO FC III patients receiving background dual therapy of an ERA + a PDE-5i: Time to first CEC confirmed MM event (up to 7 days after treatment end)						
Event	Selexipag	Placebo	Absolute Difference	HR (95% CI)		
Primary outcome first CEC-confirmed MM event, n/N (%)	41/122 (33.6%)	59/133 (44.4%)	-	0.74 (0.50, 1.10)		
Median follow up, weeks (IQR)	NR	NR	-			
% with no event at 12 months (95% CI)	79.5% (70.2, 86.1)	70.1% (61.1, 77.4)	9.4% (NR)			
Harms						
GRIPHON ITT population						
Event	Selexipag n/N	Placebo n/N	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				Selexipag	Placebo	
Treatment related AE	515/575	327/577	1.58 (1.46, 1.71)	89.6	56.7	33% (28, 38)
Death up to EOT + 7 days	46/575	37/577	1.24 (0.82, 1.89)	8.00	6.4	1.6% (-1.4, 4.6)
Prostacyclin-related AEs						
Patient with at least one event	499/575	303/577	1.65 (1.52, 1.80)	86.8	52.5	34% (29, 39)
Headache	375/575	189/577	1.99 (1.75, 2.27)	65.2	32.8	32% (27, 38)
Diarrhoea	244/575	110/577	2.25 (1.83, 2.70)	42.4	19.1	23% (18, 28)
Nausea	193/575	107/577	1.81 (1.48, 2.23)	33.6	18.5	15% (10, 20)
Pain in jaw	148/575	36/577	4.13 (2.93, 5.83)	25.7	6.2	20% (15, 24)
Vomiting	104/575	49/577	2.13 (1.55, 2.93)	18.1	8.5	10% (6, 14)
Pain in extremity	97/575	46/577	2.11 (1.52, 2.94)	16.9	8.0	9% (5, 13)
Myalgia	92/575	34/577	2.72 (1.87, 3.95)	16.0	5.9	10% (7, 14)
Flushing	70/575	29/577	2.42 (1.60, 3.67)	12.2	5.0	7% (4, 10)
Prostacyclin-related AE leading to discontinuation of study drug	59/575	11/577	5.38 (2.86, 10.14)	10.3	1.9	8% (6, 11)
Serious AEs (related to disease progression and other manifestations of underlying PAH)						
At least one SAE	252/575	272/577	1.30 (0.59, 2.89)	43.8	47.1	-3% (-9, -2)
Worsening of PAH	83/575	127/577	0.66 (0.51, 0.84)	14.4	22.0	-7% (-12, -3)

AE = adverse event; CEC = Critical Event Committee; CI = confidence interval; EOT = end of treatment; HR = hazard ratio; IQR = interquartile range; ITT = intention to treat; MM = morbidity/mortality; NR = not reported; PAH = pulmonary arterial hypertension; PBO = placebo; RD = risk difference; RR = risk ratio, CEC = Critical Event Committee,

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Source: Tables 2.27 and 2.28, pp124-125 of the submission and Tables 12-8 and 12-10, pp269-273 of GRIPHON CSR, Table B.6.4 of March 2016 commentary

- 6.30 On the basis of direct evidence presented by the resubmission, for every 100 patients treated with selexipag in comparison with placebo in a broad population of PAH patients (WHO FC I to IV), including treatment naïve, or taking background single or dual PAH therapies:
- approximately 7 patients would not have had a confirmed morbidity/mortality event at 6 months.
- 6.31 Although the results did not meet the nominal significance levels, on the basis of direct evidence presented by the resubmission, for every 100 patients treated with selexipag in comparison with placebo in patients with WHO FC III PAH and receiving background dual PAH therapy:
- approximately 9 patients would not have had a confirmed morbidity/mortality event at 12 months.
- 6.32 On the basis of direct evidence presented by the resubmission, for every 100 patients treated with selexipag in comparison with placebo in a broad population of PAH patients (WHO FC I to IV), including treatment naïve, or taking background single or dual PAH therapies over a median duration of follow-up of 70.7 and 63.7 weeks in the selexipag and placebo treatment arms, respectively:
- approximately 33 additional patients would experience treatment related adverse events (any type); and
 - approximately 34 additional patients would experience a prostacyclin-related adverse events including: headache, diarrhoea, nausea, jaw pain, vomiting, pain in extremity, myalgia and flushing.
 - approximately 8 additional patients would experience a prostacyclin-related adverse event resulting in treatment discontinuation; and
 - approximately 3 fewer patients would experience at least one serious adverse event.

Clinical claim

- 6.33 The resubmission described selexipag as superior in terms of effectiveness and inferior in terms of safety compared with placebo when used as sequential add-on therapy with ERA and a PDE-5i (i.e. triple therapy), for patients with WHO FC III or IV PAH. This claim was unchanged from the previous submissions.
- 6.34 The ESC considered the claim of superior effectiveness versus placebo in the subgroup of patients matching the PBS eligibility criteria was not adequately supported as:
- subgroup analyses of patients with WHO FC III PAH on background dual therapy with an ERA and a PDE-5i in GRIPHON did not find a statistically significant

difference between placebo and selexipag for the primary outcome of time to first CEC-confirmed MM event (up to 7 days after treatment end) (HR = 0.74; 95% CI: 0.50, 1.10). Although the ESC noted this was based on a subgroup analysis which was likely underpowered, the ESC considered that the magnitude of any benefit in patients with WHO FC III PAH remained uncertain; and

- no data was available from the GRIPHON trial to determine efficacy of sequential triple therapy of selexipag added on to background dual therapy of an ERA and a PDE-5i in patients with WHO FC IV disease. The resubmission requested listing on a high clinical need basis and argued that there is no biological rationale to consider that the relative treatment effect from triple therapy with selexipag will be significantly different in this population. The ESC considered that this statement was not adequately supported given subgroup analysis suggested potentially better efficacy for selexipag triple therapy in WHO FC II versus WHO FC III patients. The PBAC considered that although it was biologically plausible that selexipag would be beneficial in the WHO FC IV population, the magnitude of the effect was highly uncertain.

6.35 The PBAC considered that the claim of superior comparative effectiveness was likely to be reasonable.

6.36 The PBAC reaffirmed its view that the claim of inferior safety was reasonable.

Economic analysis

6.37 The resubmission presented a new stepped economic evaluation, starting with trial-based incremental cost per progression-free life year, and then implementing a modelled cost-utility analysis. This was appropriate, the March 2016 and March 2017 submissions did not present a cost-utility analysis and the PBAC had considered that a cost-utility analysis would be more informative.

6.38 Table 8 summarises the key components of the economic evaluation.

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Table 8: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Selexipag versus placebo
Time horizon	20 years in the model base case vs. ~69 weeks in the GRIPHON trial
Outcomes	QALYs
Methods used to generate results	Markov state transition model
Health states	Four health states: - Improved PAH - Stable PAH - Progressed PAH - Death
Cycle length	3 months (13 weeks)
Transition probabilities	Stable PAH / Improved PAH to Progressed PAH transition probabilities were derived from morbidity events in the GRIPHON trial (proposed PBS population).
Extrapolation method	Parametric survival functions were fitted to the Kaplan-Meier survival curve for the selexipag arm of the GRIPHON trial. The exponential distribution was selected in the base case based on best statistical fit (lowest AIC/BIC values). No mortality reduction with selexipag versus placebo was assumed. Around 81% of incremental QALYs and 30% of incremental costs occur in the extrapolated period.
Health related quality of life	Health state utilities: trial-based, derived from GRIPHON trial using CAMPHOR, a PAH-specific health-related quality of life measure. - Improved PAH = 0.727 - Stable PAH = 0.61 - Progressed PAH = 0.432 Disutility associated with IV administration of epoprostenol: literature-based (0.307) Disutility associated with severe AEs: literature based (headache, myalgia, pain 0.069, diarrhoea 0.047, nausea 0.048, oedema peripheral 0.06, syncope 0.041, pneumonia 0.2, sepsis 0.61).
Proportion of patients hospitalised upon disease progression	61.2%, based on hospitalisation and morbidity events from the GRIPHON trial (proposed PBS population).
Mean number of hospitalisations in the Progressed PAH health state	2 per patient per year, based on Hospital Episode Statistics data (England).
Proportion of patients switching to IV epoprostenol upon disease progression	80%, based on clinical expert opinion.

AE = adverse event; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; IV = intravenous; PAH = pulmonary arterial hypertension; PBS = Pharmaceutical Benefits Scheme; QALY = quality adjusted life year

Source: constructed during the evaluation.

6.39 The model comprised four health states: Improved PAH, Stable PAH, Progressed PAH and death. The base case analysis is based on the GRIPHON subgroup of patients with WHO FC III symptoms and taking dual background therapy at baseline. Patients initiate either selexipag or placebo as a new add-on therapy to their existing background therapy (dual therapy with an ERA and a PDE-5i).

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6.40 Table 9 summarised the key drivers of the economic evaluation. The main drivers of the model were disease progression probabilities, the proportion of patients receiving IV epoprostenol upon disease progression and the disutility assigned to IV epoprostenol.

Table 9: Key drivers of the model

Description	Method/Value	Impact Base case: \$45,000 to \$75,000/QALY gained.
Probability of disease progression (which determines transitions into the Progressed PAH health state)	<p>Informed by morbidity events in the GRIPHON primary composite morbidity-mortality outcome for patient in the WHO FC III and receiving background dual therapy with an ERA and a PDE-5i subgroup.</p> <p>The rate of disease progression was assumed to remain constant for the entire model duration of 20 years. The ESC and PBAC considered that this was not clinically plausible given that the morbidity events were observed in the GRIPHON trial over a median duration of only 1.3 years and due to the progressive nature of the disease.</p> <p>The model also assumed the probability of transitioning from Stable PAH to Progressed PAH was the same as the probability of transitioning from Improved PAH to Progressed PAH. The ESC and PBAC considered that it would be more reasonable to assume patients with Improved PAH have a lower probability of progression compared to those with Stable PAH.</p>	Uncertain, but likely to favour selexipag
Proportion of patients receiving IV epoprostenol upon disease progression = 80%	<p>Informed by clinical experts in PAH management. While no current Australian data on use of prostacyclin post triple therapy with selexipag was found, utilisation data sourced suggested current utilisation of prostacyclin's to be low in Australia and overseas. The PSCR states that all high risk WHO FC IV patients are offered IV epoprostenol and the 2015 ESC/ERS PAH guidelines strongly recommend IV epoprostenol as a last-line treatment option.</p> <p>The PBAC considered that there was considerable uncertainty in the proportion of patients that would progress to require IV epoprostenol and that an estimate of 50% was more reasonable (see paragraph 6.45).</p>	Very high, favours selexipag. Assuming 22.6% instead of 80% received IV epoprostenol increased the ICER to \$105,000 to \$200,000/QALY.
Disutility of IV administration of epoprostenol = 0.307	<p>Informed by Davies et al 2018, which reported utility weights associated with different modes of drug administration (i.e. oral versus non oral) for drugs acting on the prostacyclin pathway in PAH. Based on the model, patients in the Progressed PAH health state and on IV epoprostenol treatment would have a utility of 0.125 which is implausibly low. Although the ESC considered that the use of IV epoprostenol would be associated with a disutility, the ESC considered that the resultant utility of patients in the Progressed PAH patients and receiving IV epoprostenol (0.125) was implausibly low.</p> <p>The PBAC considered that the disutility decrement of 0.307 for IV epoprostenol was implausibly large and considered that a decrement of 0.1535 would be more reasonable (see paragraph 6.49).</p>	High, favours selexipag. Removing the annual disutility of IV epoprostenol in the model, increased the ICER to \$75,000 to \$105,000/QALY.

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Description	Method/Value	Impact Base case: \$45,000 to \$75,000/QALY gained.
Proportion of patients hospitalised upon disease progression = 61.2%	Informed by proportion of patients hospitalised upon morbidity event (weighted average across selexipag and placebo) for PBS subgroup ^a from post hoc analysis of GRIPHON trial.	Moderately high, favours selexipag. Assuming 48% instead of 61.2% hospitalised, increased the ICER to \$45,000 to \$75,000/QALY.
Mean number of hospitalisations per patient per year = 2	Informed by Hospital Episode Statistics data in England (Beaudet et al 2019), which was unable to be independently validated. A retrospective hospital database study in France (Bergot et al 2019) was used to support multiple hospitalisations per year. The model costed all hospitalisations, initial and subsequent, using a single hospitalisation cost of \$8,551, which may be inappropriate as subsequent hospitalisations can include day admissions for monitoring. The PBAC considered a mean number of hospitalisations per patient per year of 0.375 was reasonable. The PBAC also considered that the cost of hospitalisation may be conservative for those hospitalisation events where IV epoprostenol is initiated, given the likely duration of stay (see paragraph 6.51).	Moderately high, favours selexipag. Assuming 0.375 ^b instead of 2 hospitalisations per patient per year, increased the ICER to \$45,000 to \$75,000/QALY.
Cost for selexipag (and assumptions around wastage)	Based on dosages used in the GRIPHON trial. The resubmission estimated an average titration utilisation of 1.65 packs of the 200 mcg x 140 tablets initial pack and 0.65 packs of the 800 mcg initiation pack. However greater quantities are available on the PBS (3 for 200mcg, 140 pack and 4 for 800mcg, 60 pack). The pre-PBAC response included a revised price offer of an effective AEMP of \$ [redacted] for the initiation and maintenance packs ([redacted] % reduction).	Moderately high, favours selexipag A sensitivity analysis assuming selexipag patients would obtain the maximum number of initial packs prescribed assuming 1 + 2 repeats of the 200 mcg and 1 + 3 repeats of the 800 mcg packs increased the ICER to \$75,000 to \$105,000/QALY.

AEMP = approved ex-manufacturer price; ERA = endothelin receptor antagonist; ESC = Economic Sub-Committee; ESC/ERS = European Society of Cardiology/European Respiratory Society; FC = functional class; ICER = incremental cost effectiveness ratio; IV = intravenous; PAH = pulmonary arterial hypertension; PBAC = Pharmaceutical Benefits Advisory Committee; PDE-5i = phosphodiesterase type 5 inhibitor; PSCR = pre-Sub-Committee response; QALY = quality adjusted life year; TTO = time trade-off; WHO = World Health Organisation

^a WHO FC III and on dual therapy.

^b 0.375 hospitalisations per patient per year, based on the Beaudet et al. 2019 abstract, which had 1.4 hospitalisations per patient over a mean follow-up period of 44.8 months. Following the PBAC meeting it was identified that the 1.4 hospitalisation was the average per year not the average over the 44.8 month follow-up period.

Source: constructed during the evaluation.

6.41 All patients enter the model in the Stable PAH health state (assumed to be equivalent to WHO FC III). The ESC considered that this was not appropriate as data from the PHSANZ registry examined as part of the PMR for PAH medicines indicated approximately 6% of the cohort had entered the registry with WHO FC IV symptoms (Item 9.1 PMR PAH Attachment 1.3 Term of Reference 2 medicine utilisation analysis). In addition, the model did not include specific data for patients with WHO FC IV PAH, as they comprised only 1% of the GRIPHON trial population. Instead, the resubmission assumed that results for WHO FC III would also apply to WHO FC IV patients, based on the argument that there is no biological rationale to consider that the relative treatment effect from triple therapy with selexipag will be significantly different in this population. As discussed above, the PBAC considered that this statement was not

adequately supported given evidence for WHO FC II patients suggests a potentially different treatment effect for selexipag in that population.

- 6.42 Patients were assumed to move from Stable PAH to Improved PAH only when a new treatment was initiated; hence, this transition applied only to the first cycle of the model (25.2% of selexipag and 16.9% of placebo patients moved to the Improved PAH health state based on subgroup results from GRIPHON in patients who were WHO FC III and receiving background dual therapy who improved to WHO FC II by Week 16). The same analysis also reported that 6.8% of selexipag patients and 1.7% placebo patients experienced disease worsening to WHO FC IV by Week 16, which was not incorporated in the model. The resubmission stated that the application of improved PAH in the model was conservative as it did not incorporate further improvements in WHO FC transitions beyond Week 16. The ESC considered that WHO FC improvements after Week 16 would be unlikely.
- 6.43 Patient progression from both the Stable PAH and Improved PAH health states to the Progressed PAH health state was informed by morbidity events (hospitalisation for worsening of PAH, disease progression, initiation of IV prostanoid therapy or long-term oxygen therapy for worsening of PAH and need for lung transplantation or balloon atrial septostomy for worsening of PAH) from the primary composite morbidity-mortality endpoint in GRIPHON for the subgroup of patients with WHO FC III and receiving background dual therapy. The PBAC had previously considered the reduction in morbidity events for selexipag in GRIPHON was largely driven by hospitalisations and escalation of treatment. The model was highly sensitive to the rate of progression and the components included in the composite morbidity outcome. The PSCR stated that the components of the morbidity event are clinically appropriate markers for disease progression that indicate a clinically significant worsening of PAH. In addition, patients who met one of the component endpoints were no longer followed up for subsequent outcomes, despite remaining at risk of experiencing these events resulting in a bias against selexipag. The ESC agreed and considered that each component of the combined morbidity event would reasonably represent disease progression.
- 6.44 Other assumptions relating to progression to the Progressed PAH state disease that were potentially inappropriate included that the:
- rate of disease progression will remain constant over the model time horizon (20 years). The ESC considered that this was not clinically plausible given the progressive nature of the disease, natural factors (e.g. patient age) and as the morbidity events observed in GRIPHON were reported over a median duration of only 1.3 years; and
 - probability of transitioning from the Stable PAH to the Progressed PAH was the same as the probability of transitioning from the Improved PAH to the Progressed PAH. The ESC considered that it would be more reasonable to assume patients with Improved PAH may have a lower probability of progressing compared to those with

Stable PAH. The pre-PBAC response noted that if a lower transition rate was used for progression from Improved PAH to Progressed PAH, this would improve the cost effectiveness of selexipag.

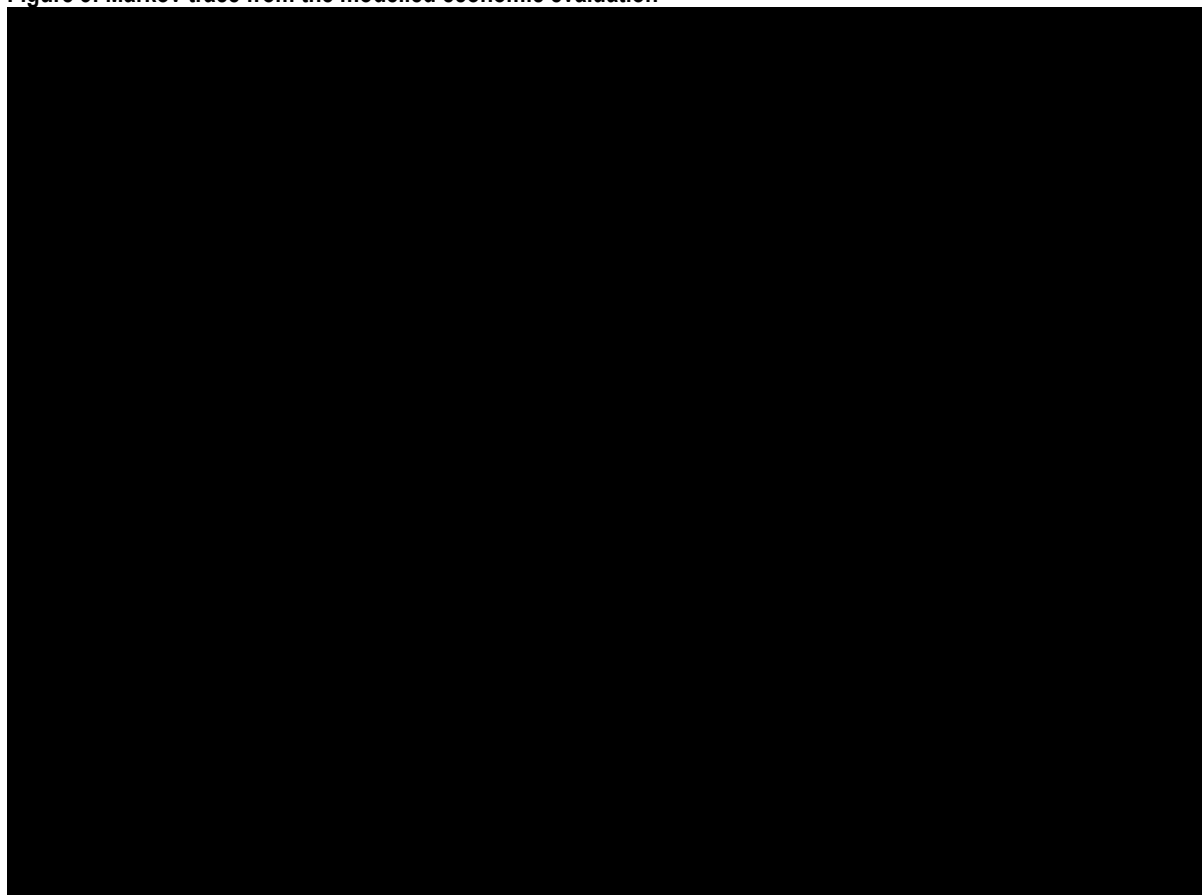
- 6.45 Patients remained on initial therapy (i.e. selexipag or placebo) until they transitioned to the Progressed PAH health state. Based on advice provided by the sponsor from clinical experts in PAH management, the model assumes that, upon disease progression, patients would cease selexipag and 80% would initiate IV epoprostenol (in addition to background dual therapy). Current PBS restrictions allow IV epoprostenol as monotherapy only in patients with WHO FC IV. In addition, although no current Australian data on the use of prostacyclins after failing triple therapy with selexipag was able to be sourced during the evaluation, available utilisation data for IV epoprostenol and inhaled iloprost indicates the use of prostacyclins is low in Australia and overseas. The overall proportion of patient's prescribed triple therapy in the PHSANZ registry cohort was 10.4% (Item 9.1 PMR PAH Attachment 1.3 Term of Reference 2 medicine utilisation analysis). A retrospective analysis of a large health care claims database in the USA (Burger et al 2018²), where there are less funding restrictions on combination therapies in PAH, indicated the rates of prostacyclin use to be less than 25%. The PSCR stated that the utilisation figure from Burger et al 2018 (< 25%) was not applicable as it represented the use of prostacyclins in the whole PAH population, not in WHO FC IV patients. With regards to the PHSANZ data, the PSCR stated that 5.9% of the cohort were WHO FC IV. Given that epoprostenol is PBS listed for patients with WHO FC IV PAH only, the proportion of patients in the registry with WHO FC IV was lower than the proportion of patients receiving IV epoprostenol (10.4%). Although the PSCR suggested that this data was supportive of the clinical expert advice that 80% was a reasonable estimate, the ESC noted that this suggested either inconsistency in the data or usage of IV epoprostenol outside of the eligible population. The ESC considered that there was a significant discordance in the PHSANZ data and considered that the 80% estimation was likely too high. The PSCR also stated that expert clinical advice indicated that all high risk WHO FC IV patients are offered IV epoprostenol and the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) PAH guidelines strongly recommend IV epoprostenol as a last-line treatment option where other therapies are no longer able to control progressive disease. In the GRIPHON trial, 1.7% and 2.2% of selexipag and placebo patients respectively required parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH, although the ESC noted the number of WHO FC IV patients in the trial was low (n = 6). The ESC considered that as the model was highly sensitive to the proportion of patients receiving IV epoprostenol, further data on its use in Australia would better inform the economic model. The pre-PBAC response

² Burger CD, Pruettt JA, Lickert C A, et al. Prostacyclin use among patients with pulmonary arterial hypertension in the United States: a retrospective analysis of a large health care claims database. *Journal of Managed Care & Specialty Pharmacy*. 2018;24(3);291-302.

provided data from a published retrospective chart review of an Australian PAH clinic (Feenstra et al, 2019) which estimated the utilisation of prostacyclins in WHO FC IV PAH ranged from 47.8% to 86.7% (depending on how patients were included in the analysis). The PBAC considered that an estimate of 50% would be more reasonable.

- 6.46 The model did not include an improvement in overall survival between selexipag and placebo because the ITT analysis of the GRIPHON trial did not demonstrate a statistically significant survival gain by the end of the trial period. The ESC noted this may have been conservative given the results of the landmark analysis by McLaughlin et al 2018, but considered that this was countered by the lack of a statistically significant benefit in the requested population (WHO FC III PAH and receiving background dual therapy) in the GRIPHON trial. Overall, the ESC considered that the lack of modelled survival benefit was appropriate. Parametric survival functions (exponential, Weibull, log-logistic and log-normal) were fitted to the Kaplan Meier survival curve of the selexipag arm of the GRIPHON trial to estimate the transition probabilities from the PAH health states to death. The exponential distribution was selected for the base case, as it had the best statistical fit (lowest AIC/BIC values). As no mortality difference was assumed between the selexipag and placebo arms and as the same mortality extrapolations were applied to both arms, survival is not a driver of the model.
- 6.47 The model traces of the proportions of patients in the Improved PAH, Stable PAH, and Progressed PAH health states over time, are presented in Figure 3.

Figure 3: Markov trace from the modelled economic evaluation



Source: constructed during the evaluation.

- 6.48 The utility weights for the Stable PAH (0.610) and Improved PAH (0.727) health states were derived from the baseline utilities by WHO FC in the GRIPHON trial, which used a PAH-specific Health related quality of life (HRQoL) measure assessing impairment, disability and quality of life: Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR). Due to lack of data on WHO FC IV patients in the GRIPHON trial, the difference in utility for the Progressed PAH health state compared to the Stable health state (0.178) was estimated using the average difference in utility between WHO FC III and IV and WHO FC II and III. This was then subtracted from the Stable PAH health state utility to estimate a utility of 0.432 for Progressed PAH. The resubmission did not validate the model's quality of life assumptions against broader literature. Data from an alternate publication (that was also identified by the resubmission), Keogh et al 2007, reported smaller differences between the different PAH classes and a much higher health state utility for Progressed PAH (i.e. Improved PAH: 0.67, Stable PAH: 0.60 and Progressed PAH: 0.52). The ICER increased to \$45,000 to \$75,000 per QALY from a base case of \$45,000 to \$75,000 when these alternate utilities were used.
- 6.49 The disutility of continuous IV administration of epoprostenol for patients in the Progressed PAH state was informed by Davies et al 2018, which reported utility weights associated with different modes of drug administration (i.e. oral versus non

oral) for drugs acting on the prostacyclin pathway in PAH. The resubmission assumed that IV epoprostenol resulted in a disutility of 0.307, which is larger than other estimates in the literature associated with IV infusions. The application of this result in the model could lead to double counting of the disutility as the health state utility for Progressed PAH included events such as initiation of IV epoprostenol. Based on the model, patients in the Progressed PAH health state and on IV epoprostenol treatment would have a utility of 0.125 (i.e. 0.432 - 0.307). The PSCR considered that the disutility was not double counted as the proportion of patients in the GRIPHON trial receiving IV epoprostenol was very low (1.7% in the selexipag arm and 2.2% in the placebo arm); therefore, the results of these patients would not have significantly influenced the quality of life outcomes. In terms of the disutility decrement of 0.307, the PSCR stated that Davies et al 2018 is the only published PAH specific utility study, that patients with WHO FC IV PAH are unable to carry out any physical activity without exhibiting a worsening of symptoms and that many patients experience significant discomfort at rest. The ESC recognised that IV epoprostenol would be associated with some additional disutility, but also felt that symptom improvement could occur in the proportion of patients who benefited. The ESC considered that the utility of 0.125 for patients with progressed PAH and receiving IV epoprostenol was implausibly low. The pre-PBAC response noted that the model assumed 30% of patients receiving IV epoprostenol would experience an improvement in quality of life, and that for these patients the utility decrement of 0.307 was subtracted from the Stable PAH state utility, resulting in a utility of 0.303 (i.e. 0.610 - 0.307). Thus, the net utility for progressed PAH patients on IV EPO in the model ranged from 0.125 to 0.303. The PBAC noted the advice from ESC that the model inputs should be conservative (paragraph 6.58). The PBAC also acknowledged that IV epoprostenol can have a significant impact on quality of life, but considered that the sensitivity analysis in the ESC advice in which the utility decrement associated with IV epoprostenol was removed to be extreme. Overall, the PBAC considered that the utility decrement applied in the resubmission of 0.307 was large and that a reasonable estimate would be 0.1535 (i.e. half that assumed in the resubmission).

- 6.50 The model applied a hospitalisation rate of 61.2% to all patients transitioning to the Progressed PAH health state, calculated as the proportion of total hospitalisation events over total morbidity events in each arm of the GRIPHON trial. The resubmission did not present real life data to validate this value. A USA study (Burger et al. 2015) sourced during the evaluation reported a rate of hospitalisation of 48% for WHO FC IV patients newly diagnosed with PAH.
- 6.51 The model assumed the mean number of PAH-related hospitalisations per patient per year to be 2.0, based on Hospital Episode Statistics (HEC) data in England (Beaudet et al, 2019). The PBAC noted that Beaudet et al 2019 reported a mean of 1.4 inpatient admissions per patient over 44.8 months or 0.375 admissions per year. Following the PBAC meeting it was identified that the 1.4 hospitalisation was the average per year not the average over the 44.8 month follow-up period. The resubmission cited a

retrospective hospital database study in France (Bergot et al, 2019) to support multiple hospitalisations per year for PAH. Bergot et al 2019 reported 3.3 hospitalisations per year; however, approximately half of the hospital stays in the patient cohort were classified as monitoring stays, with day admissions accounting for around a third of all hospitalisations. The model applied a single cost of \$8,551 per hospitalisation for both initial and subsequent hospitalisations. The hospitalisation cost was derived using the average cost per day from the National Hospital Cost Data Collection based on Australian Refined Diagnosis Related Group codes mapped from pulmonary hospitalisation International Classification of Diseases codes, assuming an average length of stay of 4.6 days for primary pulmonary hypertension. The PBAC considered that the rate of hospitalisation was overestimated and should not include day admissions/outpatient visits for monitoring or supervised medication changes. The PBAC considered a more reasonable estimate to be 0.375 admissions per year. The PBAC also considered that the cost of hospitalisation may have been underestimated for those hospitalisation events where IV epoprostenol was initiated, as patients could be admitted for longer periods of time at the commencement of IV therapy.

- 6.52 Other healthcare costs in the model include (i) drug cost for selexipag, (ii) costs of background PAH therapies (ERA and PDE-5i), (iii) costs of subsequent PAH therapies i.e. IV epoprostenol, (iv) PAH disease management costs by health states, (v) costs of morbidity events (with and without hospitalisation), (vi) mortality event/death cost and (vii) costs of severe adverse events.
- 6.53 Selexipag drug costs were estimated based on dosages in the GRIPHON trial. For titration, the resubmission estimated an average utilisation of 1.65 packs (maximum 2 packs) of the 200 mcg x 140 tablets initiation pack and 0.65 packs of the 800 mcg initiation pack.
- 6.54 Although the time horizon was 20 years, the model only demonstrated minimal sensitivity to extensions of the time horizon beyond 10 years (ICERs of \$45,000 to \$75,000, \$45,000 to \$75,000, and \$45,000 to \$75,000 per QALY at 10, 15 and 25 years respectively) but was more sensitive when the time horizon was reduced to less than 10 years (ICERs of \$45,000 to \$75,000 and \$75,000 to \$105,000 per QALY at 7 and 5 years). As evident in the Markov trace (Figure 3), this is because by 10 years, most patients in the model had transitioned into the Progressed PAH health state, which is a key driver of the model.
- 6.55 Tables 10 and 11 summarise the disaggregated healthcare resource item costs and health outcomes from the modelled economic evaluation. Incremental costs associated with selexipag versus placebo were driven by the cost of selexipag. The largest cost offsets were associated with disease progression, especially the cost of IV epoprostenol (including administration costs), and hospitalisation for morbidity events. Patients in the selexipag arm spent more time in the Stable PAH and Improved PAH health states and less time in the Progressed PAH health state compared to the

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placebo arm. The ICER was sensitive to progression rates and the proportion of progressed patients receiving IV epoprostenol.

Table 10: Health care resource items: disaggregated summary of cost impacts

Resource item	Selexipag arm	Placebo arm	Incremental cost	% of total incremental cost
Drug costs including selexipag titration costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
Selexipag costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
Selexipag titration healthcare costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
Background therapy drug costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
Epoprostenol drug costs	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]	[REDACTED]%
Other costs				
Hospitalisation cost of initiating IV epoprostenol	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]	[REDACTED]%
PAH disease management costs	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]	[REDACTED]%
Morbidity event hospitalisation costs	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]	[REDACTED]%
Morbidity event costs without hospitalisation	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]	[REDACTED]%
Hospitalisation cost for mortality event	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
Costs of adverse events	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]	[REDACTED]%
TOTAL COSTS (undiscounted)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
TOTAL COSTS (discounted)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%

IV = intravenous; PAH = pulmonary arterial hypertension

Source: Table 3.35, p193 of the resubmission; Attachment 10 of resubmission.

Table 11: Disaggregated summary of health outcomes included in the economic evaluation

Outcome (undiscounted)	Selexipag arm	Placebo arm	Incremental outcome	% of total incremental outcome
Improved PAH (utility 0.727)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]%
Stable PAH (utility 0.61)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]%
Progressed PAH (utility 0.432)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]%
AE-specific utility (disutility)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]%
Drug admin utility (disutility)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]%
Total QALYs (undiscounted)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]%
Total QALYs (discounted)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]%

AE = adverse event; PAH = pulmonary arterial hypertension; QALY = quality adjusted life year

Source: Table 3.36, p193 of the resubmission.

6.56 Table 12 presents the results of the stepped economic evaluation which was estimated based on the subgroup results from the GRIPHON trial for WHO FC III patient receiving dual therapy at baseline. The base case ICER was \$45,000 to \$75,000 per QALY. Reducing the price of selexipag as per the pre-PBAC response (i.e. to \$ [REDACTED] per pack) reduced the ICER to \$15,000 to \$45,000 per QALY.

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Table 12: Results of the stepped economic evaluation

Step and component	Selexipag	Placebo	Increment
Step 1: Trial-based analysis (69 weeks): WHO FC III + background dual therapy subgroup from GRIPHON			
<u>Costs:</u> drug costs for selexipag and background therapies, costs for nurse and doctor visits during selexipag dose titration			
<u>Outcomes:</u> Progression free life years for those who survive and did not have a morbidity outcome adjusted for mean time on treatment			
Costs	\$ [REDACTED]	\$ [REDACTED]*	\$ [REDACTED]
Progression-free life years	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/additional progression-free life year			\$ [REDACTED]*
Step 2: Trial based analysis over 69 weeks			
As for Step 1 <u>plus:</u>			
- Added % of patients with improvement in WHO FC at Week 16			
- Calculation of mean time spent in each health state (Improved, Stable, Progressed and Dead)			
- Applied health state utility weights to estimate QALYs			
- Added drug and administration costs for IV epoprostenol based on the assumption that 80% of patients will initiate treatment upon entering the Progressed health state			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 3: Modelled economic evaluation (time horizon 20 years)^			
As for Step 2 <u>plus:</u>			
- Extrapolation of trial based survival to 20-year using the exponential survival function;			
- addition of health state costs associated with management of PAH;			
- inclusion of costs and disutility associated with treatment-related serious AEs;			
- inclusion of disutility associated with treatment administration method			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained (base case)			\$ [REDACTED]
Incremental cost/extra QALY gained (pre-PBAC base case)			\$ [REDACTED]

AE = adverse event; FC = functional class; IV = intravenous; PAH = pulmonary arterial hypertension; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality adjusted life year; WHO = World Health Organisation

* Corrected for transcription error for background therapy costs (values in cells N14 and O14 in Attachment 15 – Selexipag Stepped Econ Evaluation were corrected to \$8,760 as per the economic model instead of \$8,921), this resulted in slight change to estimated costs for the placebo arm in the Step 1 results.

^ Derived from Attachment 10 of the resubmission – Selexipag Economic Model Final.

Source: Table 3.34, p192 of the resubmission; Attachment 15 – Selexipag Stepped Econ Evaluation.

- 6.57 Table 13 presents the results of key univariate and multivariate sensitivity analyses. The ICER was most sensitive to the proportion of patients receiving IV epoprostenol upon disease progression and the application of the disutility for IV epoprostenol.
- 6.58 The ESC, noting the limitations of the clinical data (i.e. no data for patients with WHO FC IV PAH) and the uncertainty surrounding the magnitude of benefit in patients with WHO FC III PAH, along with structural issues around application of progression rates in the model, considered that the model inputs should be conservative. The ESC suggested a number of univariate and multivariate sensitivity analyses which may be informative and which, although not addressing the structural issues, demonstrated the uncertainty of the model. The PBAC agreed with the ESC that there were structural issues with the model as well as uncertainty with the economic model reliability, which was illustrated by the high degree of sensitivity of the model to various inputs.

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Table 13: Results of key sensitivity analyses, updated to incorporate the pre-PBAC response effective AEMP of selexipag (\$ [redacted] per initiation and maintenance pack)

Sensitivity analyses	Incremental costs	Incremental QALY	ICER per QALY
Base case as presented in submission (AEMP \$ [redacted])	\$ [redacted]	[redacted]	\$ [redacted]
Base case with pre-PBAC response price (AEMP \$ [redacted])	\$ [redacted]	[redacted]	\$ [redacted]
Univariate analyses (incorporating pre-PBAC response price)			
Probability of transitioning from Stable PAH and Improved PAH to Progressed PAH health state over the 20 year time horizon (base case: selexipag = 0.067; placebo = 0.1)			
- Selexipag = 0.033; placebo = 0.05 (probabilities = 1/2 of base case)	\$ [redacted]	[redacted]	\$ [redacted]
- Selexipag = 0.044; placebo = 0.067 (probabilities = 2/3 of base case)	\$ [redacted]	[redacted]	\$ [redacted]
Mean number of hospitalisations per patient per year (base case: 2 per year)			
- 3.3 hospitalisations per patient per year, based on French retrospective hospital database study (Bergot et al 2019)	\$ [redacted]	[redacted]	\$ [redacted]
- 1.4 hospitalisations per patient per year, based on reported number in Beaudet et al. 2019	\$ [redacted]	[redacted]	\$ [redacted]
- 1.4 hospitalisations per patient over a mean follow-up period of 44.8 months, or 0.375 hospitalisations per patient per year, based on Beaudet et al. 2019	\$ [redacted]	[redacted]	\$ [redacted]
Cost of hospitalisation (base case: \$8,551)			
- \$12,048 (DRG cost with major complications)	\$ [redacted]	[redacted]	\$ [redacted]
- \$3,205 (DRG cost with minor complications)	\$ [redacted]	[redacted]	\$ [redacted]
- No hospitalisation cost	\$ [redacted]	[redacted]	\$ [redacted]
Proportion receive IV epoprostenol upon disease progression (base case: 80%)			
- 100%	\$ [redacted]	[redacted]	Dominant
- 50%	\$ [redacted]	[redacted]	\$ [redacted]
- 22.6%, based on upper range of annual prevalence of prostacyclin use from Burger et al. 2018	\$ [redacted]	[redacted]	\$ [redacted]
Disutility of IV administration of epoprostenol (base case: 0.307)			
- Removal of disutility for IV administration of epoprostenol	\$ [redacted]	[redacted]	\$ [redacted]
Multivariate analyses (incorporating pre-PBAC response price)			
- 50% receive IV epoprostenol upon disease progression, PLUS - 1.4 hospitalisations per patient per year	\$ [redacted]	[redacted]	\$ [redacted]
- 50% receive IV epoprostenol upon disease progression, PLUS - 1.4 hospitalisations per patient per year, PLUS - Removal of disutility for IV administration of epoprostenol	\$ [redacted]	[redacted]	\$ [redacted]
- 50% receive IV epoprostenol upon disease progression, PLUS - 1.4 hospitalisations per patient per year, PLUS - Removal of disutility for IV administration of epoprostenol, PLUS - Transition probabilities = 2/3 of base case (selexipag = 0.044; placebo = 0.067)	\$ [redacted]	[redacted]	\$ [redacted]
- 22.6% receive IV epoprostenol upon disease progression, PLUS - 0.375 hospitalisations per patient per year	\$ [redacted]	[redacted]	\$ [redacted]
- 22.6% receive IV epoprostenol upon disease progression, PLUS - 0.375 hospitalisations per patient per year, PLUS - Removal of disutility for IV administration of epoprostenol	\$ [redacted]	[redacted]	\$ [redacted]
- 22.6% receive IV epoprostenol upon disease progression, PLUS - 0.375 hospitalisations per patient per year, PLUS - Removal of disutility for IV administration of epoprostenol, PLUS - Transition probabilities = 2/3 of base case (selexipag = 0.044; placebo = 0.067)	\$ [redacted]	[redacted]	\$ [redacted]
Multivariate analyses based on inputs recommended by the PBAC (incorporating pre-PBAC response price)			
- 50% receive IV epoprostenol upon disease progression, PLUS - 0.375 hospitalisations per patient per year, PLUS - IV epoprostenol disutility of 0.1535	\$ [redacted]	[redacted]	\$ [redacted]

AEMP = approved ex-manufacturer price; DRG = diagnostic-related group; ICER = incremental cost effectiveness ratio; IV = intravenous; PAH = pulmonary arterial hypertension; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality adjusted life year

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Source: Table 3.38, p196 of the resubmission; Attachment 10 of resubmission (EXCEL file of Section 3 model).

The redacted table shows ICERs in the range of less than \$15,000 per QALY, to more than \$200,000 per QALY.

Drug cost/patient/year

6.59 The cost of selexipag in the pre-PBAC response was \$ [redacted] (dispensed effective price, public hospital) and \$ [redacted] (dispensed effective price, private hospital) per maintenance pack of 60 tablets (all strengths). The drug cost of selexipag per patient on a twice daily dosing regimen, was \$ [redacted] per year, for a patient on maintenance treatment, at the effective DPMQ, and assuming 100% compliance and a 66% versus 34% public - private hospital split (as per the economic model). The financial estimates assumed that the proportion of patients treated in public and private hospitals was 68% and 32%, respectively, based on 2019 Medicare data for all ERAs and PDE-5is.

6.60 Table 14 compares drug costs between the trial, model and financial estimates.

Table 14: Drug cost per patient for selexipag

	Selexipag Trial dose and duration	Selexipag Model	Selexipag Financial estimates
Dose/day	200 mcg bd to 1600 mcg bd depending on IMD	200 mcg bd to 1600 mcg bd depending on IMD	200 mcg bd to 1600 mcg bd depending on IMD
Cost/patient/month (maintenance) ^a	-	\$ [redacted] ^b	\$ [redacted] ^c
Cost/patient/year (maintenance) ^a	-	\$ [redacted] ^b	\$ [redacted] ^c

bd = twice daily; ERA = endothelin receptor antagonist; IMD = individualised maintenance dose; PDE-5i = phosphodiesterase type 5 inhibitor.

^a Calculated as: 14 tablets per week (twice daily dosing) x 52 weeks in a year x cost per tablet (weighted average cost weighted for public and private use).

^b Assumed 66% public use and 34% private use (source could not be verified).

^c Assumed 68.2% public use and 32.8% private use (sourced from 2019 Medicare data for all ERAs and PDE-5is).

Source: constructed during the evaluation.

Estimated PBS usage & financial implications

6.61 This resubmission was not considered by DUSC. The resubmission presented revised financial implications based on a market share approach to estimate the eligible population using updated Medicare data, and accounting for selexipag use as add-on to dual therapy and accounting for selexipag titration use. Table 15 presents the key inputs for financial estimates.

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Table 15: Key inputs for financial estimates

Parameter	Value applied and source	Comment
% on dual therapy	40% - 65% based on Scenario 3a, PBAC's review of PMR for PAH Medicines, November 2019	Reasonable.
Uptake rate	█% in Year 1 increasing to █% in Year 6. Based on assumptions.	Likely underestimated; similar to estimates used in previous submissions. Pre-PBAC Response: increased uptake rate to █% in Year 1, increasing to █% in Year 6.
Growth rate of ERA and PDE-5i market	Year 1: 100% Year 2: 75% Year 3: 70% Year 4: 65% Year 5: 60% Year 6: 55%	The resubmission claimed that the market growth rate appears to have slowed during 2016-2019, thus the 2018-2019 growth rate was applied and then the growth rate was increasingly slowed down. The resubmission stated that this was to best match the DoH estimates. Closer inspection of the Medicare data showed that although the market slowed in 2016, the market appeared to steadily increase thereafter to 2019. The March 2016 submission assumed linear growth from 2017 to 2021. The ESC considered that the market growth rates were likely underestimated. The pre-PBAC response maintained that the projected market growth was appropriate. The PBAC noted recent PBS utilisation data which suggested that utilisation was likely to increase.
Selexipag titration duration	6.8 weeks based on GRIPHON doses and estimates in the modelled economic evaluation.	Consistent with the durations in the economic evaluation. An issue identified by the March 2016 submission was estimates not accounting for use and cost of selexipag during the dose titration (para 6.54, selexipag, PSD, March 2016). This has now been incorporated.
Selexipag titration packs per patient	1.65 based on economic model.	Consistent with the economic evaluation.
Phone call appointment with specialist nurse	MBS item 10983	Appropriate.
GP visits	MBS item 36	Appropriate.
Effective AEMP	200 mcg initiation pack: \$ █ Maintenance packs: \$ █	Pre-PBAC response: 200 mcg initiation pack and all maintenance packs reduced \$ █

AEMP = approved ex-manufacturer price; DoH = Department of Health; ERA = endothelin receptor antagonist; ESC = Economic Sub-Committee; GP = general practitioner; MBS = Medicare Benefits Schedule; PAH = pulmonary arterial hypertension; PBAC = Pharmaceutical Benefits Advisory Committee; PDE-5i = phosphodiesterase type 5 inhibitor; PMR = post market review; PSD = Public Summary Document. Source: constructed during the evaluation.

6.62 The ESC considered that the estimated net cost to PBS as presented in the resubmission was likely underestimated due to:

- potential changes in the estimated market share of PAH drugs as a result of forthcoming PBS listing of PAH therapies in dual therapy and the expansion of listing in monotherapy to WHO FC II patients; and
- the assumption of a decline in the growth rate of the total ERA and PDE-5i market over time. The PBAC noted that recent PBS utilisation data suggest utilisation is likely to increase.

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6.63 Table 16 presents the revised estimated use and financial implications of listing selexipag on the PBS as presented in the pre-PBAC. As noted in Table 15, these estimates include an increased uptake of selexipag (increasing from █% to █% over 5 years; changed from █% to █% in the resubmission; the uptake in year 6 was unchanged at █%) but the growth rate is the same as presented in the resubmission.

Table 16: Estimated use and financial implications (incorporating pre-PBAC response price of selexipag of \$█ per pack and updated uptake rates)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed ^a	█	█	█	█	█	█
Estimated financial implications of selexipag						
Cost to PBS/RPBS less copayments	\$█	\$█	\$█	\$█	\$█	\$█
Estimated financial implications for other medicines						
Cost to PBS/RPBS less copayments	-	-	-	-	-	-
Net financial implications						
Net cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to MBS	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to PBS/RPBS/MBS	\$█	\$█	\$█	\$█	\$█	\$█
Submission base case						
Net cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to MBS	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to PBS/RPBS/MBS	\$█	\$█	\$█	\$█	\$█	\$█
Previous submission (March 2017)						
ERA and PDE-5i patients						-
Selexipag patients						-
Net cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	-

ERA = endothelin receptor antagonist; MBS = Medicare Benefits Schedule; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PDE-5i = phosphodiesterase type 5 inhibitor; RPBS = Repatriation Pharmaceutical Benefits Scheme.

Source: Table 4.3, p203 of resubmission; Tables 4.7-4.12, pp. 207-209 of resubmission.

^a Ambrisentan PBS private item numbers 9648T and 9649W have been added into the analysis, and total ambrisentan growth rate from 2018-2019 adjusted to 6.4% with the inclusion of these items.

The redacted table shows that at Year 6, the estimated number of scripts dispensed was 10,000 to 50,000.

6.64 The total cost to the PBS/RPBS of listing selexipag was estimated to be \$20 million to \$30 million in Year 6, and a total of \$60 million to \$100 million over the first 6 years of listing.

6.65 The ESC considered a Risk Sharing Arrangement (RSA) may be appropriate to manage the uncertainty in the patient population and the proposed use in patients for which there is very limited data (e.g. in WHO FC IV PAH patients and patients unable to tolerate dual therapy). The pre-PBAC response proposed an RSA with a █ rebate for expenditure above the revised net cost to the PBS/RPBS estimates.

Quality Use of Medicines

- 6.66 The resubmission noted the need for instructions regarding the up-titration and dose tolerability effects. The additional risk minimisation activities involve providing every prescriber with a prescriber kit containing the approved product information, the Consumer Medicines Information, a letter to the physician, a laminated physician titration card, and a patient titration card. These activities were described in the Risk Management Plan. In addition, the Sponsor is planning one-on-one interactions with the prescribers to educate them on patient selection criteria and PBS listing restrictions, and peer-to-peer education sessions between clinicians.

7 PBAC Outcome

- 7.1 The PBAC recommended the Section 85 (General Schedule) - Authority Required (delayed assessment) listing of selexipag for the treatment patients with World Health Organisation (WHO) Functional Class (FC) III or IV pulmonary arterial hypertension (PAH). The recommendation for selexipag was as triple therapy in combination with an endothelin receptor antagonist (ERA) and a phosphodiesterase-5 inhibitor (PDE-5i), with an exception permitting dual therapy in combination with an ERA or PDE-5i in a small number of patients who are intolerant or contraindicated to one of these classes of therapies. The PBAC was satisfied that selexipag provides, for some patients, a significant improvement in efficacy over placebo. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of selexipag would be acceptable if the incremental cost effectiveness ratio (ICER) was less than \$80,000 per quality adjusted life year (QALY) gained for the revised economic model scenario as described in paragraph 7.12 below.
- 7.2 The PBAC noted the views expressed in the sponsor hearing, and the comments from individuals, health care professionals and organisations that outlined the extent to which PAH limits daily activities and impairs quality of life. The comments also described the reduced quality of life associated with continuous intravenous (IV) infusion of epoprostenol and the risk of pump or administration line failures, and that treatment with selexipag may delay or avoid the need for treatment with IV epoprostenol. The PBAC considered that an orally-acting prostacyclin agent would provide a substantial benefit to patients.
- 7.3 The Committee reaffirmed its view that placebo (as combination therapy with an ERA and a PDE-5i) was the appropriate comparator.
- 7.4 The PBAC noted the submission relied on the GRIPHON trial, a Phase III, randomised, placebo controlled trial of selexipag across all WHO functional classes, and post-hoc subgroup analyses of the GRIPHON data for patients receiving dual ERA/PDE-5i background therapy. The primary outcome was a composite morbidity-mortality event comprising of death, hospitalisation for PAH worsening, parenteral prostanoid or chronic oxygen therapy, PAH worsening resulting in the need for lung transplantation or balloon atrial septostomy or disease progression events.

- 7.5 The PBAC noted that for the intention to treat population of GRIPHON, which comprised of a broad population of patients with WHO FC I to IV disease who were receiving a range of background therapies, selexipag was associated with a 39% reduction in the risk of the primary endpoint (HR = 0.61; 99% CI: 0.46, 0.81). The PBAC noted that, although the result for patients with WHO FC III PAH who were receiving dual background therapy was not statistically significant (HR = 0.74; 95% CI: 0.50, 1.10), the point estimate favoured selexipag and was consistent with the ITT population result. The PBAC considered that the subgroup analysis was underpowered and that the lack of statistical significance was likely due to a Type II error.
- 7.6 The PBAC noted that no data were presented for patients with WHO FC IV PAH due to insufficient sample size (n=6). Whilst the PBAC considered that it was biologically plausible that selexipag would be beneficial in this patient population, particularly considering the effect of other prostacyclins in these patients, the PBAC noted the greater effect of selexipag in less severe WHO FC II PAH patients compared to in those with WHO FC III disease.
- 7.7 The PBAC noted the landmark analysis by McLaughlin 2018 that investigated the prognostic relevance of PAH morbidity for mortality. The PBAC noted that mortality events occurred at a substantially higher rate in patients who experienced morbidity events at 3, 6 and 12-month time points. The PBAC considered there may be a mortality benefit associated with a reduction in morbidity or disease progression events.
- 7.8 Based on the evidence presented, the PBAC considered the claim that selexipag, when used in combination with an ERA and a PDE-5i in patients with WHO FC III and IV PAH, was superior to placebo was reasonable, but that the magnitude of the benefit remained uncertain.
- 7.9 The PBAC noted no new clinical data on comparative harms was presented and recalled that it had previously considered that selexipag was inferior to placebo with regards to comparative safety. The Committee noted that many of the adverse events were consistent with those for other medicines which act on the prostacyclin pathway and that the long titration period with selexipag is designed to manage these events.
- 7.10 The PBAC noted that the resubmission appropriately presented a trial-based, stepped economic evaluation which resulted in a modelled cost-utility analysis. The model utilised four health state (Improved PAH, Stable PAH, Progressed PAH and Death) and a time horizon of 20 years. The modelled population was based on the GRIPHON subgroup of patients with WHO FC III symptoms and receiving dual background therapy at baseline.
- 7.11 The base case ICER presented in the resubmission was \$45,000 to \$75,000 per QALY gained. The PBAC noted ESC's concerns regarding the modelled evaluation, including the limitations of the clinical data (i.e. no data for patients with WHO FC IV PAH), uncertainty surrounding the magnitude of benefit in patients with WHO FC III PAH, and structural issues around the application of progression rates in the model. The

PBAC further noted the high degree of uncertainty for a number of the key model inputs, including the proportion of patients treated with IV epoprostenol upon disease progression, the reduced quality of life (disutility) associated with IV epoprostenol treatment and the assumed number of PAH related hospitalisations. The PBAC considered that the results of the univariate and multivariate analyses demonstrated a high degree of sensitivity to these inputs. The PBAC agreed with ESC and considered that, given the model uncertainties, the inputs for the base case analysis should be conservative.

7.12 The PBAC noted the reduced price of selexipag proposed in the pre-PBAC response reduced the ICER for the resubmission's base case from \$45,000 to \$75,000 to \$15,000 to \$45,000 per QALY gained, however considered this ICER to be unreliable given the issues noted above. The PBAC considered the key model inputs would be appropriately conservative if they were re-specified as follows:

- the proportion of patients receiving IV epoprostenol upon disease progression is reduced from 80% to 50% based on the lower bound as calculated in the pre-PBAC response using data from a retrospective chart review of an Australian PAH clinic (Feenstra et al, 2019);
- the PBAC acknowledged that IV epoprostenol can have a significant impact on patients' quality of life; however, considered that the utility decrement applied in the resubmission of 0.307 appeared large. The PBAC considered that a reasonable conservative estimate would be 0.1535 (i.e. half that assumed in the resubmission);
- the number of PAH related hospitalisations per patient per year is reduced from 2 to 0.375 based on the mean number of inpatient admissions as reported in Beudet et al 2019. Following the PBAC meeting it was identified that the rate of 0.375 hospitalisation per year incorrectly assumed that hospitalisations were averaged over the 44.8 month follow-up period rather than 1 year. The PBAC considered that the rate of 2 hospitalisations per year assumed in the submission, and the rate of 1.4 per year reported in the Beudet et al 2019 conference abstract, to be higher than expected in Australian clinical practice.

7.13 The PBAC noted that the above changes increased the ICER from \$15,000 to \$45,000 to \$75,000 to \$105,000 per QALY gained. The PBAC considered that an acceptable ICER, using the re-specified model, would be an ICER of less than \$80,000 per QALY gained.

7.14 Regarding the financial estimates, the PBAC noted ESC's concerns with respect to the growth rate of the ERA and PDE-5i market, and the percent of dual treatment to which selexipag would be added (uptake). The pre-PBAC response maintained that the reduced growth rate over time as applied in the resubmission was reasonable. To address the concerns raised during the evaluation and by ESC, the uptake was increased in the pre-PBAC response (increasing from ■% to ■% over 5 years; changed from ■% to ■% in the resubmission; uptake in year 6 was unchanged at

- █%). The PBAC considered the revised uptake as presented in the pre-PBAC response to be reasonable, noting its recommendation for the listing is to include patients with WHO FC IV PAH and dual therapy and that the uptake should not be further increased to account for these patients.
- 7.15 To address the overall clinical and financial uncertainty associated with the proposed population, an RSA was proposed in the pre-PBAC response with subsidisation caps based on the revised financial estimates and a rebate of █ of the cost of selexipag for use above the subsidisation caps. The rebate level was justified in the pre-PBAC response on the basis that selexipag has been shown to be effective in a broader patient population than the proposed PBS restriction in the GRIPHON trial. Noting the uncertainty in clinical effectiveness in the populations for which there was little or no data, the PBAC considered the rebate for use above the caps should be at least █. The PBAC also noted the price reduction required to achieve an acceptable ICER (paragraph 7.13) would flow through to the subsidisation caps.
- 7.16 In terms of the proposed restrictions for selexipag as triple therapy, the PBAC noted that the proposed listing includes combination use with the ERAs ambrisentan and macitentan, but not bosentan. The PBAC disagreed that bosentan should be excluded as one of the eligible ERAs which could be used in combination with a PDE-5i, noting that it had previously considered that the potential drug-drug interactions and safety concerns of the bosentan plus PDE-5i combination were well managed by clinicians.
- 7.17 The PBAC noted that the listing of selexipag as triple therapy could not be finalised prior to the listing of ERA plus PDE-5i dual therapy.
- 7.18 The PBAC noted there would be flow-on restriction changes to the listings of the ERAs and PDE-5i medicines to facilitate triple therapy.
- 7.19 The PBAC advised that selexipag should not be treated as interchangeable with any other drugs.
- 7.20 The PBAC advised that selexipag is not suitable for prescribing by nurse practitioners.
- 7.21 The PBAC recommended that the Early Supply Rule should apply.
- 7.22 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that the circumstances of its recommendation for selexipag:
- a) Treatment with selexipag is expected to provide a clinically relevant improvement in efficacy over alternative therapies with respect to treating PAH.
 - b) Treatment with selexipag is not expected to address a high and urgent unmet clinical need because other subsidised therapies are available;
 - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

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7.23 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new medicinal product as follows (indicative listing shown below; details still to be finalised):

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
SELEXIPAG					
selexipag 200 microgram tablet, 140	NEW	1	1	2	Uptravi
selexipag 800 microgram tablet, 60	NEW	1	1	3	Uptravi

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Episodicity: [blank]
Severity: [blank]
Condition: Pulmonary arterial hypertension (PAH)
PBS Indication: Pulmonary arterial hypertension (PAH)
Treatment phase: Dose titration
Restriction type / method: <input checked="" type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart)
Treatment criteria:
Treatment must be for dose titration purposes with the intent of completing the titration within 12 weeks
AND
Clinical criteria:
Patient must have been assessed by a physician with expertise in the management of PAH
AND
Clinical criteria:
Patients must have documented WHO Functional Class III PAH or WHO Functional Class IV PAH
AND
Clinical criteria:
The treatment must form part of triple combination therapy with a PBS-subsidised phosphodiesterase-5 inhibitor (PDE-5i) together with a PBS-subsidised endothelin receptor antagonist (ERA); or
The treatment must form part of dual combination therapy with one of the above mentioned drug classes, but only when triple combination therapy is not possible due to at least one of the following being present: (i) a contraindication according to the TGA approved Product Information, (ii) an intolerance requiring permanent treatment cessation
AND
Clinical criteria:
The treatment must be in addition to existing dual therapy with a phosphodiesterase-5 inhibitor (PDE-5i) agent combined with an endothelin receptor antagonist (ERA) for pulmonary arterial hypertension (PAH); or
The treatment must be in addition to existing therapy with a phosphodiesterase-5 inhibitor (PDE-5i)/an endothelin receptor antagonist (ERA) for pulmonary arterial hypertension (PAH), but only when dual ERA-PDE-5i combination therapy was not possible due to at least one of the following being present: (i) a contraindication according to the TGA approved Product Information, (ii) an intolerance requiring permanent treatment cessation
AND
Clinical criteria:
The treatment must not be as monotherapy

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<p>Prescriber Instructions: PAH (WHO Group I pulmonary hypertension) is defined as follows: (i) mean pulmonary artery pressure (mPAP) greater than or equal to 25 mmHg at rest and pulmonary artery wedge pressure (PAWP) less than or equal to 15 mmHg; or (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>Prescriber Instructions: 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>
<p>Prescriber Instructions: Delayed assessment instructions (to be determined)</p>
<p>Administrative advice: PAH (WHO Group 1 pulmonary hypertension) currently includes the following subtypes:</p> <ul style="list-style-type: none"> • Idiopathic PAH • Heritable PAH <ul style="list-style-type: none"> o BMPR2 mutation o ALK-1, ENG, SMAD9, CAV1, KCNK3 mutations o Other mutations • Drugs and toxins induced PAH • PAH associated with: <ul style="list-style-type: none"> o Connective tissue disease o Human immunodeficiency virus (HIV) infection o Portal hypertension o Congenital heart disease o Schistosomiasis
<p>Administrative advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au</p> <p>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos</p> <p>Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
<p>Administrative Advice: The relevant agency assessing a first-time authority application for this drug is to confirm that there is valid, active authority approval for both an endothelin receptor (ERA) antagonist and phosphodiesterase-5 inhibitor (PDE-5i). A concurrently lodged/yet to be assessed application for PBS subsidy of either will not suffice for the purpose of this restriction. Where triple therapy combination is not possible, confirm that that there is a valid authority approval for at least one of an ERA or PDE-5i.</p>
<p>Administrative Advice: Special Pricing Arrangements apply</p>
<p>Administrative Advice: No increase in the maximum quantity or number of units may be authorised.</p>
<p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>

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Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
SELEXIPAG					
selexipag 200 microgram tablet, 60	NEW	1	1	5	Uptravi
selexipag 400 microgram tablet, 60	NEW	1	1	5	Uptravi
selexipag 600 microgram tablet, 60	NEW	1	1	5	Uptravi
selexipag 800 microgram tablet, 60	NEW	1	1	5	Uptravi
selexipag 1,000 microgram tablet, 60	NEW	1	1	5	Uptravi
selexipag 1,200 microgram tablet, 60	NEW	1	1	5	Uptravi
selexipag 1,400 microgram tablet, 60	NEW	1	1	5	Uptravi
selexipag 1,600 microgram tablet, 60	NEW	1	1	5	Uptravi

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Episodicity: N/A
Severity: [blank]
Condition: Pulmonary arterial hypertension (PAH)
PBS Indication: Pulmonary arterial hypertension (PAH)
Treatment phase: Initial treatment (non-dose titration)
Restriction type: <input checked="" type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart)
Clinical criteria:
Patient must have been assessed by a physician with expertise in the management of PAH
AND
Clinical criteria:
Patient must have documented WHO Functional Class III PAH or WHO Functional Class IV PAH at treatment initiation with this drug
AND
Clinical criteria:
The treatment must form part of triple combination therapy with a PBS-subsidised phosphodiesterase-5 inhibitor (PDE-5i) together with a PBS-subsidised endothelin receptor antagonist (ERA); or
The treatment must form part of dual combination therapy with one of the above mentioned drug classes, but only when triple combination therapy is not possible due to at least one of the following being present: (i) a contraindication according to the TGA approved Product Information, (ii) an intolerance requiring permanent treatment cessation
AND
Clinical criteria:
The treatment must be in addition to existing dual therapy with a phosphodiesterase-5 inhibitor (PDE-5i) agent combined with an endothelin receptor antagonist (ERA) for pulmonary arterial hypertension (PAH); or
The treatment must be in addition to existing therapy with a phosphodiesterase-5 inhibitor (PDE-5i)/an endothelin receptor antagonist (ERA) for pulmonary arterial hypertension (PAH), but only when dual ERA-PDE-5i combination therapy was not possible due to at least one of the following being present: (i) a contraindication according to the TGA approved Product Information, (ii) an intolerance requiring permanent treatment cessation
AND
Clinical criteria:
The treatment must not be as monotherapy
Prescriber Instructions:
PAH (WHO Group I pulmonary hypertension) is defined as follows: (i) mean pulmonary artery pressure (mPAP) greater than or equal to 25 mmHg at rest and pulmonary artery wedge pressure (PAWP) less than or equal to 15 mmHg; or (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.
Prescriber Instructions:
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.

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<p>Prescriber Instructions: Delayed assessment instructions (to be determined)</p>
<p>Administrative Advice: PAH (WHO Group 1 pulmonary hypertension) currently includes the following subtypes:</p> <ul style="list-style-type: none"> • Idiopathic PAH • Heritable PAH <ul style="list-style-type: none"> o BMPR2 mutation o ALK-1, ENG, SMAD9, CAV1, KCNK3 mutations o Other mutations • Drugs and toxins induced PAH • PAH associated with: <ul style="list-style-type: none"> o Connective tissue disease o Human immunodeficiency virus (HIV) infection o Portal hypertension o Congenital heart disease o Schistosomiasis
<p>Administrative advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au</p> <p>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos</p> <p>Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
<p>Administrative Advice: The relevant agency assessing a first-time authority application for this drug is to confirm that there is valid, active authority approval for both an endothelin receptor (ERA) antagonist and phosphodiesterase-5 inhibitor (PDE-5i). A concurrently lodged/yet to be assessed application for PBS subsidy of either will not suffice for the purpose of this restriction. Where triple therapy combination is not possible, confirm that that there is a valid authority approval for at least one of an ERA or PDE-5i.</p>
<p>Administrative Advice: Special Pricing Arrangements apply</p>
<p>Administrative Advice: No increase in the maximum quantity or number of units may be authorised.</p>
<p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Episodicity: N/A
Severity: [blank]
Condition: Pulmonary arterial hypertension (PAH)
PBS Indication: Pulmonary arterial hypertension (PAH)
Treatment phase: Continuing treatment
Restriction type: <input checked="" type="checkbox"/> Authority Required –immediate/real-time assessment by Services Australia (telephone/online)
Clinical criteria:
Patient must have been assessed by a physician with expertise in the management of PAH
AND
Clinical criteria:
Patient must have received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition

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AND
Clinical criteria:
The treatment must form part of triple combination therapy with a PBS-subsidised phosphodiesterase-5 inhibitor (PDE-5i) together with a PBS-subsidised endothelin receptor antagonist (ERA); or
The treatment must form part of dual combination therapy with one of the above mentioned drug classes, but only when triple combination therapy is not possible due to at least one of the following being present: (i) a contraindication according to the TGA approved Product Information, (ii) an intolerance requiring permanent treatment cessation
AND
Clinical criteria:
The treatment must not be as monotherapy
Prescriber instructions:
For the purposes of administering this restriction, disease progression has developed if at least one of the following has occurred: (i) Hospitalisation due to worsening PAH; (ii) If measured, deterioration of aerobic capacity/endurance (a 15% decrease or more in 6-Minute Walk Distance (6MWD) from baseline), plus worsening of WHO functional class status or need for additional PAH-specific therapy; (iii) Initiation of parenteral prostanoid therapy or long-term oxygen therapy for worsening of PAH; (iv) Need for lung transplantation or balloon atrial septostomy for worsening of PAH;
Administration Advice:
Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting the Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
Administrative Advice: Special Pricing Arrangements apply
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.

Flow-on changes to endothelin receptor antagonists and phosphodiesterase-5 inhibitors to permit use in triple-therapy combination treatment:

To be finalised

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.

Addendum to the July 2020 PBAC Minutes:

**4.02 SELEXIPAG,
Tablets, 200, 400, 600, 800, 1000, 1200, 1400, 1600
microgram,
Uptravi[®],
Janssen-Cilag Pty Ltd.**

11 Purpose of item

- 11.1 To seek the Committee's consideration on revising its July 2020 recommendation for a Section 85 (General Schedule) listing of selexipag to a recommendation for a Section 100 – Highly Specialised Drugs listing.

12 Background

- 12.1 At the July 2020 meeting, the PBAC recommended the Section 85 (General Schedule) - Authority Required listing of selexipag (item 7.07) for the treatment patients with World Health Organisation (WHO) Functional Class (FC) III or IV pulmonary arterial hypertension (PAH). The recommendation for selexipag was as triple therapy in combination with an endothelin receptor antagonist (ERA) and a phosphodiesterase-5 inhibitor (PDE-5i), with an exception permitting dual therapy in combination with an ERA or PDE-5i in a small number of patients who are intolerant or contraindicated to one of these classes of therapies.
- 12.2 The PBAC noted the sponsor's request was for a Section 100 – Highly Specialised Drugs (HSD) listing for selexipag as, currently, the PBS listed ERAs and PDE-5i have Section 100 HSD Program listings. The HSD Program is for drugs that are highly specialised, making administration outside an institutional environment problematic. However, the administration of selexipag outside an institution environment was considered by the PBAC to be non-problematic, as it is an orally administered drug that is unlikely to have immediate, life-threatening administration sequelae for which an institutional environment equipped with resuscitation equipment and expertise to handle an acute medical emergency, would be needed. Therefore, listing selexipag under special circumstances through the Section 100 HSD Program, was not considered appropriate (paragraph 3.12, item 7.07 selexipag PSD, July 2020).

13 Issues/Matters for the PBAC to consider

Discrepancy in access

- 13.1 While the PBAC recommended selexipag be listed under Section 85, it was noted that all other currently listed PAH drugs (oral and intravenous) are administered under

Section 100 HSD Program. The resulting inconsistency will result in dispensing impracticalities particularly for the oral PAH agents where a dual or triple therapy (with selexipag) is permitted. Patients would be required to have ERA & PDE-5i drugs dispensed at a hospital pharmacy department and subsequently be required to attend a community pharmacy to have their selexipag prescription dispensed.

- 13.2 Despite the apparent simplicity of selexipag administration, the management of PAH occurs in a specialised hospital setting and PAH medicines available under the HSD program are routinely dispensed in the hospital setting, even though the HSD program arrangements allow dispensing of these medicines both in the hospital and community setting. General schedule medicines are generally not able to be dispensed at hospital pharmacies. Equity of access issues are raised if the listing of PAH medicines were separated across the HSD and general schedule likely causing confusion for patients already at risk of safety concerns through poly-pharmacy from triple therapy.

HSD listing criteria

- 13.3 At its April 2015 Intracycle Meeting, the PBAC advised the Minister on the revised criteria for listing of HSD drugs. The PBAC considered the criteria applied by the former HSD Working Party and advised that the criterion that differentiated HSD listings from General Schedule listings was “the drug is highly specialised, making administration outside an institutional environment problematic and the patient target group is clearly identifiable”.
- 13.4 In the case of selexipag, the PBAC considered that selexipag meets the ‘highly specialised criteria’ and ‘patient target group is clearly identifiable’ criteria, but not the ‘administration outside an institutional environment problematic’ criterion, as stated in paragraph 2.2 above. Due to the nature of the conditions treated by medicines on the HSD program and the medicines themselves, potential HSD listings have historically been considered broadly on the criteria provided within the broader environment relating to the drug. The criterion for inclusion in the HSD program do not require that all criteria be met in each instance, therefore selexipag could be considered appropriate to meet an s100 HSD listing criteria in the context of the criteria stated above and in view of the overall complex hospital based management of PAH.

Sponsor/clinician feedback

- 13.5 The sponsor of selexipag contacted the Department on 1 September expressing their concerns and that of some clinicians represented by Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ) regarding the Section 85 listing for selexipag. The sponsor outlined PHSANZ’s concerns to be as follows:

Selexipag is a highly specialised drug that requires prescribing and management of patients by medical practitioners with specific knowledge and experience in PAH. Specifically,

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- the drug has the potential to cause serious harm or death if it is prescribed to the wrong subset of pulmonary hypertension patients – those with left heart disease or pulmonary hypertension secondary to interstitial lung disease,
- the drug does not have standard dosing and requires individualised titration for every patient. Incorrect dosing will result in the clinical benefit of selexipag not being realised and not cost-effective use of the drug, and
- the drug has significant side effects, and although they can be managed effectively in clinical practice, it is critical to balance these with the dosing for each individual patient, which requires clinicians with extensive experiences in PAH.

14 PBAC Outcome

- 14.1 The PBAC revised its previous recommendation to list selexipag under Section 85, and instead recommended listing selexipag under Section 100 - Highly Specialised Drugs.
- 14.2 The PBAC noted the issues identified in paragraphs 13.1 to 13.4 stated above. The PBAC agreed that there may be potential inequity in access if the listing of PAH medicines were separated across the HSD and general schedule. The PBAC considered that in this instance selexipag could be considered appropriate to meet an s100 HSD listing criteria in the context of the broader environment relating to the drug and in view of the overall complex hospital based management of PAH.
- 14.3 The PBAC also noted the concerns raised by the sponsor of selexipag and clinicians stated in paragraph 13.5.

15 Recommended Listing

- 15.1 Add new medicinal product as follows (Program/category revised. Restrictions as per the July 2020 recommendation item 7.07 selexipag):

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
SELEXIPAG					
selexipag 200 microgram tablet, 140	NEW	1	1	2	Uptravi
selexipag 800 microgram tablet, 60	NEW	1	1	3	Uptravi

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: General Schedule (Code GE) Section 100 - Highly Specialised Drugs Program (Public/Private)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Episodicity: [blank]
Severity: [blank]
Condition: Pulmonary arterial hypertension (PAH)
PBS Indication: Pulmonary arterial hypertension (PAH)
Treatment phase: Dose titration
Restriction type / method: <input checked="" type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart)
Treatment criteria:
Treatment must be for dose titration purposes with the intent of completing the titration within 12 weeks

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AND
Clinical criteria:
Patient must have been assessed by a physician with expertise in the management of PAH
AND
Clinical criteria:
Patients must have documented WHO Functional Class III PAH or WHO Functional Class IV PAH
AND
Clinical criteria:
The treatment must form part of triple combination therapy with a PBS-subsidised phosphodiesterase-5 inhibitor (PDE-5i) together with a PBS-subsidised endothelin receptor antagonist (ERA); or
The treatment must form part of dual combination therapy with one of the above mentioned drug classes, but only when triple combination therapy is not possible due to at least one of the following being present: (i) a contraindication according to the TGA approved Product Information, (ii) an intolerance requiring permanent treatment cessation
AND
Clinical criteria:
The treatment must be in addition to existing dual therapy with a phosphodiesterase-5 inhibitor (PDE-5i) agent combined with an endothelin receptor antagonist (ERA) for pulmonary arterial hypertension (PAH); or
The treatment must be in addition to existing therapy with a phosphodiesterase-5 inhibitor (PDE-5i)/an endothelin receptor antagonist (ERA) for pulmonary arterial hypertension (PAH), but only when dual ERA-PDE-5i combination therapy was not possible due to at least one of the following being present: (i) a contraindication according to the TGA approved Product Information, (ii) an intolerance requiring permanent treatment cessation
AND
Clinical criteria:
The treatment must not be as monotherapy
Prescriber Instructions:
PAH (WHO Group I pulmonary hypertension) is defined as follows: (i) mean pulmonary artery pressure (mPAP) greater than or equal to 25 mmHg at rest and pulmonary artery wedge pressure (PAWP) less than or equal to 15 mmHg; or (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.
Prescriber Instructions:
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.
Prescriber Instructions:
Delayed assessment instructions (to be determined)
Administrative advice:
PAH (WHO Group 1 pulmonary hypertension) currently includes the following subtypes: <ul style="list-style-type: none"> • Idiopathic PAH • Heritable PAH <ul style="list-style-type: none"> o BMPR2 mutation o ALK-1, ENG, SMAD9, CAV1, KCNK3 mutations o Other mutations • Drugs and toxins induced PAH • PAH associated with: <ul style="list-style-type: none"> o Connective tissue disease o Human immunodeficiency virus (HIV) infection o Portal hypertension o Congenital heart disease o Schistosomiasis
Administrative advice:
Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au
Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos
Or mailed to:

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Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Administrative Advice: The relevant agency assessing a first-time authority application for this drug is to confirm that there is valid, active authority approval for both an endothelin receptor (ERA) antagonist and phosphodiesterase-5 inhibitor (PDE-5i). A concurrently lodged/yet to be assessed application for PBS subsidy of either will not suffice for the purpose of this restriction. Where triple therapy combination is not possible, confirm that there is a valid authority approval for at least one of an ERA or PDE-5i.
Administrative Advice: Special Pricing Arrangements apply
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
SELEXIPAG					
selexipag 200 microgram tablet, 60	NEW	1	1	5	Uptravi
selexipag 400 microgram tablet, 60	NEW	1	1	5	Uptravi
selexipag 600 microgram tablet, 60	NEW	1	1	5	Uptravi
selexipag 800 microgram tablet, 60	NEW	1	1	5	Uptravi
selexipag 1,000 microgram tablet, 60	NEW	1	1	5	Uptravi
selexipag 1,200 microgram tablet, 60	NEW	1	1	5	Uptravi
selexipag 1,400 microgram tablet, 60	NEW	1	1	5	Uptravi
selexipag 1,600 microgram tablet, 60	NEW	1	1	5	Uptravi

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: General Schedule (Code GE) Section 100 - Highly Specialised Drugs Program (Public/Private)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Episodicity: N/A
Severity: [blank]
Condition: Pulmonary arterial hypertension (PAH)
PBS Indication: Pulmonary arterial hypertension (PAH)
Treatment phase: Initial treatment (non-dose titration)
Restriction type: <input checked="" type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart)
Clinical criteria:
Patient must have been assessed by a physician with expertise in the management of PAH
AND
Clinical criteria:
Patient must have documented WHO Functional Class III PAH or WHO Functional Class IV PAH at treatment initiation with this drug
AND
Clinical criteria:
The treatment must form part of triple combination therapy with a PBS-subsidised phosphodiesterase-5 inhibitor (PDE-5i) together with a PBS-subsidised endothelin receptor antagonist (ERA); or
The treatment must form part of dual combination therapy with one of the above mentioned drug classes, but only when triple combination therapy is not possible due to at least one of the following being present: (i) a contraindication according to the TGA approved Product Information, (ii) an intolerance requiring permanent treatment cessation
AND
Clinical criteria:
The treatment must be in addition to existing dual therapy with a phosphodiesterase-5 inhibitor (PDE-5i) agent combined with an endothelin receptor antagonist (ERA) for pulmonary arterial hypertension (PAH); or
The treatment must be in addition to existing therapy with a phosphodiesterase-5 inhibitor (PDE-5i)/an endothelin receptor antagonist (ERA) for pulmonary arterial hypertension (PAH), but only when dual ERA-PDE-5i combination

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therapy was not possible due to at least one of the following being present: (i) a contraindication according to the TGA approved Product Information, (ii) an intolerance requiring permanent treatment cessation
AND
Clinical criteria:
The treatment must not be as monotherapy
Prescriber Instructions: PAH (WHO Group I pulmonary hypertension) is defined as follows: (i) mean pulmonary artery pressure (mPAP) greater than or equal to 25 mmHg at rest and pulmonary artery wedge pressure (PAWP) less than or equal to 15 mmHg; or (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.
Prescriber Instructions: 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.
Prescriber Instructions: Delayed assessment instructions (to be determined)
Administrative Advice: PAH (WHO Group 1 pulmonary hypertension) currently includes the following subtypes: <ul style="list-style-type: none"> • Idiopathic PAH • Heritable PAH <ul style="list-style-type: none"> o BMPR2 mutation o ALK-1, ENG, SMAD9, CAV1, KCNK3 mutations o Other mutations • Drugs and toxins induced PAH • PAH associated with: <ul style="list-style-type: none"> o Connective tissue disease o Human immunodeficiency virus (HIV) infection o Portal hypertension o Congenital heart disease o Schistosomiasis
Administrative advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Administrative Advice: The relevant agency assessing a first-time authority application for this drug is to confirm that there is valid, active authority approval for both an endothelin receptor (ERA) antagonist and phosphodiesterase-5 inhibitor (PDE-5i). A concurrently lodged/yet to be assessed application for PBS subsidy of either will not suffice for the purpose of this restriction. Where triple therapy combination is not possible, confirm that there is a valid authority approval for at least one of an ERA or PDE-5i.
Administrative Advice: Special Pricing Arrangements apply
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: General Schedule (Code GE) Section 100 - Highly Specialised Drugs Program (Public/Private)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Episodicity: N/A
Severity: [blank]

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Condition: Pulmonary arterial hypertension (PAH)
PBS Indication: Pulmonary arterial hypertension (PAH)
Treatment phase: Continuing treatment
Restriction type: <input checked="" type="checkbox"/> Authority Required –immediate/real-time assessment by Services Australia (telephone/online)
Clinical criteria:
Patient must have been assessed by a physician with expertise in the management of PAH
AND
Clinical criteria:
Patient must have received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
The treatment must form part of triple combination therapy with a PBS-subsidised phosphodiesterase-5 inhibitor (PDE-5i) together with a PBS-subsidised endothelin receptor antagonist (ERA); or
The treatment must form part of dual combination therapy with one of the above mentioned drug classes, but only when triple combination therapy is not possible due to at least one of the following being present: (i) a contraindication according to the TGA approved Product Information, (ii) an intolerance requiring permanent treatment cessation
AND
Clinical criteria:
The treatment must not be as monotherapy
Prescriber instructions:
For the purposes of administering this restriction, disease progression has developed if at least one of the following has occurred:
(i) Hospitalisation due to worsening PAH;
(ii) If measured, deterioration of aerobic capacity/endurance (a 15% decrease or more in 6-Minute Walk Distance (6MWD) from baseline), plus worsening of WHO functional class status or need for additional PAH-specific therapy;
(iii) Initiation of parenteral prostanoid therapy or long-term oxygen therapy for worsening of PAH;
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17 Sponsor's Comment

The sponsor had no comment.