Response to Terms of Reference
PAH Post-market Review
27th March 2017

Introduction

GlaxoSmithKline (GSK) recognises the Government's responsibility to maintain a robust Pharmaceutical Benefits Scheme (PBS), and we further recognise that Post Market Reviews (PMRs) can play a role in ensuring the Quality Use of Medicines (QUM) accessed via the PBS.

GSK welcomes constructive collaboration with the Department and the PBAC on the Pulmonary Arterial Hypertension (PAH) PMR to address any agreed genuine concerns, which are supported by data or medical professional advice. We are also committed to contributing to this review our technical knowledge and expertise on the important PAH medicines we supply through the PBS to Australian patients.

Scope

Terms of Reference

Accepting the available information, GSK has provided a short summary of feedback for consideration.

1. ***Review recent clinical guidelines for the management of PAH and compare this to the PBS restrictions and Therapeutic Goods Administration (TGA) indications for the use of PAH medicines.***

   The GSK sponsored medicines included in this review are ambrisentan (Volibris®) and epoprostenol (Flolan®). Table 1 summarises the recommendations provided for each of these GSK medicines, in regards to the clinical guidelines, PBS restrictions and TGA indications.
   It is noted that whilst no local Australian clinical guidelines exist for PAH, there are two applicable international guidelines, including:
   - 'Updated treatment algorithm of pulmonary arterial hypertension' (Galie, JACC 2013[1]), which presents the updated treatment algorithm endorsed at the 5th World Symposia on Pulmonary Hypertension (PH), a meeting which is held every 5 years, and
   - 'Guidelines for the diagnosis and treatment of pulmonary hypertension' (Galie, ESC/ERS 2015[2]).

   GSK considers the ESC/ERS 2015 guidelines to be the most relevant for the purposes of the PMR as they incorporate the latest evidence for combination therapy.

Table 1: Summary of PBS restrictions, TGA indications and clinical guideline recommendations

Medicine	Guidelines	PBS restriction	TGA indication
Ambrisentan	The ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension emphasise that the overall treatment goal for patients with PAH is achieving a low risk status which means bringing and/or keeping the patient in WHO FC II wherever possible. For patients at a low or intermediate risk of clinical worsening or death (ie. those patients in WHO FC I-III) treatment with either monotherapy or initial combination therapy is recommended. Since head-to-head comparisons among different compounds are not available, no evidence-based first-line monotherapy can be recommended, however, a hierarchy has been proposed according to the level of evidence regarding efficacy. In these patients, ambrisentan monotherapy has been assigned a Class I/Level A recommendation in FC II and III and a Class IIb/Level C recommendation in FC IV**. The combination of tadalafil and ambrisentan is the ONLY combination with a class I recommendation for upfront combination therapy in FC II and III PAH patients.[2]*** This is based on the results of the	Patient must have WHO Functional Class III or IV Idiopathic pulmonary arterial hypertension (iPAH) or anorexigen-induced PAH or hereditable PAH OR Patient must have WHO Functional Class III or IV pulmonary arterial hypertension secondary to connective tissue disease. The treatment must be the sole PBS-subsidised PAH agent for this condition#	Volibris monotherapy is indicated for the treatment of: idiopathic pulmonary arterial hypertension (PAH) and PAH associated with connective tissue disease (PAH-CTD), in patients with WHO functional class II, III or IV symptoms. Volibris in combination with tadalafil is indicated for the treatment of WHO Group 1 PAH in patients with WHO functional class II, III or IV symptoms.[4]

	AMBITION trial which found that the combination of ambrisentan and tadalafil demonstrated a significantly lower risk of clinical-failure events than the risk with pooled ambrisentan and tadalafil monotherapy alone.[3]		
Flolan	The ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension recommend that for patients at high risk of clinical worsening or death (WHO FC IV patients), initial combination therapy including I.V. prostacyclin analogues should be considered. I.V. epoprostenol should be prioritised since it reduced the 3-month rate of mortality in high-risk PAH patients also as monotherapy. In PAH patients with WHO FC III and IV symptoms, I.V. epoprostenol has been given a class IA recommendation for efficacy of monotherapy.[2]	Patient must have WHO Functional Class IV idiopathic pulmonary arterial hypertension (iPAH), anorexigen-induced PAH or hereditable PAH OR Patient must have WHO Functional Class IV pulmonary arterial hypertension secondary to connective tissue disease. Patient must have WHO Functional Class III idiopathic pulmonary arterial hypertension (iPAH) or anorexigen-induced PAH or hereditable PAH or PAH secondary to connective tissue disease and must have failed to respond to a prior PBS-subsidised PAH agent. The treatment must be the sole PBS subsidised PAH agent for this condition.#	Flolan is indicated for the long-term treatment, via continuous intravenous infusion, in WHO functional class III or class IV patients with: Idiopathic pulmonary arterial hypertension; Familial pulmonary arterial hypertension; Pulmonary arterial hypertension associated with the scleroderma spectrum of diseases.[5]

Abbreviations: ESC/ERS: European Society of Cardiology/European Respiratory Society; FC: functional class; I.V: intravenous; PAH: pulmonary arterial hypertension; PBS: pharmaceutical benefits scheme.

Note: PBS restriction is abridged for purposes of simplicity in table

**ERS/ESC Guideline Recommendations (Class-Level) regarding ERA monotherapy and epoprostenol (adapted from ERS/ESC Guidelines 2015[2])

	WHO FC II	WHO FC III	WHO FC IV
Ambrisentan	I-A	I-A	IIb-C
Bosentan	I-A	I-A	IIb-C
Macitentan	I-B	I-B	IIb-C
Epoprostenol	-	I-A	I-A

***ERS/ESC Guideline Recommendations (Class-Level) regarding initial combination therapy (adapted from ERS/ESC Guidelines 2015[1])

	WHO FC II	WHO FC III	WHO FC IV
Ambrisentan/tadalafil	I-B	I-B	IIb-C

Other ERA + PDE-5i	IIa-C	IIa-C	IIb-C
Bosentan + sildenafil + i.v. epoprostenol	-	IIa-C	IIa-C
Bosentan + i.v. epoprostenol	-	IIa-C	IIa-C
Other ERA or PDE-5i + s.c. treprostinil	-	IIb-C	IIb-C
Other ERA or PDE-5i + other i.v. prostacyclin analogues	-	IIb-C	IIb-C

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.

2. ***Review the utilisation of PAH medicines in Australia, including sources of data that can provide additional information on clinical use that is not available from PBS data.***

In order to address this particular ToR, it may be beneficial to consider data sources available through the Pulmonary Hypertension Society of Australia & New Zealand (PHSANZ), a not for profit organisation with a mandate to advocate for a sustainable 'model of care' with equitable access to skilled clinicians that allows timely diagnosis, treatment and ongoing management for patients with PH in Australia and New Zealand. An early focus of the Society was to set up a National PH registry, which provides a platform for research and improves our understanding of PH. The registry offers comprehensive insights into the current demographics of the patient population and mortality based on aetiologies of PH and first treatment. The most recently published report (3rd annual report, Oct 2015) is available via the following link:
http://www.phsanz.com.au/Portals/0/downloads/PHSANZ%202015%20Registry%20report%20Oct%202015%20final.pdf

In a recent DUSC analysis (February 2015) it was noted that in practice, combination therapy is achieved by adding low cost private prescription sildenafil to another of the PBS subsidised drugs.

In light of this insight, GSK has completed its own analysis of the extent of use of PDE-5 inhibitor sildenafil by reviewing IMS data (which captures all sales to retail and hospital pharmacies including direct from manufacturer) in conjunction with PBS prescription data for the year 2016. The following products were included in the analysis: Revatio, Sildenafil PHT AN, Sildenafil SDZ PHT, Sildenafil-DRX and APO-Sildenafil PHT. A ratio of 1.92 was calculated

representing the total number of sildenafil units (20mg, 90) for PAH indications accessed through IMS compared to PBS prescriptions, and implies that twice the volume of units are accessed outside of the PBS system. These results demonstrate the considerable need for combination treatment and highlight the current limitations imposed by the PBS on restricting use of PAH therapies to sole therapy only.

In order to address the apparent inequality in accessing combination therapy, GSK has developed a MedAccess Program which provides clinicians an interim mechanism to access combination treatment in the form of an ERA (ambrisentan) and PDE-5 inhibitor (tadalafil). Combination therapy of ambrisentan and tadalafil has been granted the highest grade recommendation of evidence (Class I) for naive PAH patients in the ERS/ESC 2015 guidelines based on robust clinical evidence generated by the AMBITION trial.[2] Clinicians have expressed their support for the program, particularly as the combination available is reflective of international clinical practice guidelines.

GSK recognises that whilst combination therapy is not currently subsidised through the PBS, providing timely and sustainable access to this treatment option is pertinent, hence the Company is reviewing whether it is possible to address this unmet clinical need via a submission to the PBS.

3. ***Review the clinical outcomes that are most important or clinically relevant to patients with PAH, and the extent to which these outcomes are included in the evidence previously considered by PBAC.***

There have been significant advances in the field of PAH over the last 2 decades which has seen a shift in focus from short-term functional changes to improvements in long-term outcomes.[6] Historically, clinical trials in PAH have used the change in six minute walk distance (6MWD) as a primary efficacy endpoint yet its suitability as an indicator of long-term prognosis remains unclear.[2,6-8] Accordingly, current guidelines recommend a comprehensive assessment of patients, acknowledging that no single variable provides sufficient diagnostic and prognostic information alone. In recognition of this, current treatment goals now include bringing/keeping the patient in WHO FC I or II, 6MWD >440m, normalisation of right ventricular size and function on echocardiograph/cardiac magnetic resonance imaging, a decreasing or normalisation of B-type Natriuretic Peptide (BNP) level and haemodynamics showing normalisation of right ventricular function with right ventricular pressure (RAP) <8mmHg and cardiac index (CI) ≥2.5l/min/m^2.[2,6]

As such, when it comes to demonstrating efficacy of newer PAH agents, it was recommended by the Task Force on End Points and Clinical Trial Design at the 4th World Symposium on PH, that composite endpoints of disease progression including mortality and morbidity measures be used as primary endpoints in phase III trials.[7] It was recommended that these endpoints should include the following: all-cause mortality, non elective hospital stay (with pre-defined criteria, usually the initiation of I.V. prostanoids, lung transplantation or atrial septostomy) and disease progression (defined as a reduction from baseline in 6MWD by 15% and worsening

of WHO functional class); and that these should be adjudicated by an independent committee.[7,8] The need to adopt a morbidity and mortality primary endpoint in phase III trials was further confirmed at the 5th World Symposium on PH with affirmation that it more comprehensively reflects clinically meaningful treatment effects.[9]

In recognition of this, GSK's phase III AMBITION trial used a robust definition of morbidity/mortality measures termed 'time to clinical failure' which incorporated the recommendations of the Task Force and further refined them to include a more stringent definition of PAH worsening via inclusion of the component 'Unsatisfactory long-term clinical response', which was defined as "**ANY** decrease from baseline in 6MWD at 2 consecutive clinic visits after baseline separated by at least 14 days, and WHO functional class III symptoms assessed at 2 clinic visits separated by at least 6 months".[3]

The evidence considered by the PBAC in past submissions such as bosentan, sildenafil and ambrisentan included change in six minute walk test (6MWT) as the primary efficacy outcome, with secondary outcomes comprising change in WHO functional class, time to clinical worsening and Borg dyspnoea index. More recent submissions however have included composite morbidity/mortality endpoints which the PBAC have considered as more patient relevant. In its review of macitentan, 'The PBAC considered the time to first mortality/morbidity event a more patient relevant outcome than the 6MWD' (Opsumit® (macitentan), Public Summary Document March 2014).

The clinical relevance of the outcomes previously assessed however are justified given the evidence was deemed appropriate and acceptable to support inclusion of these treatments on the PBS.

4. ***Collate and evaluate evidence on the comparative effectiveness of PAH medicines, including combination use and use in the WHO functional class II patient populations.***

PAH is classified as a rare orphan disease therefore the opportunity to conduct head to head trials via traditional methods is very limited. There are a limited number of subjects available to enter trials and they are generally isolated in a few tertiary care centres. Large head-to-head trials in PAH would require significant patient numbers, which would result in extended enrolment timelines and consequently inflated study costs.

Thus, there are currently few head-to-head randomised controlled trials (RCT) that assess the comparative efficacy and safety of PAH treatments; and also few high-quality comparative studies to assess the long-term efficacy and safety of PAH drug therapies.

Nonetheless, table 2 outlines the available evidence for ambrisentan and epoprostenol that is yet to be considered by the PBAC with inclusion of studies pertaining to combination use and use in the FC II patient population:

Table 2: Summary of clinical evidence

GSK Product	Name of Study	Details of Study
Volibris + Tadalafil	AMBITION Initial combination therapy with ambrisentan and tadalafil in patients with WHO Group 1 PAH FC II/III Galie N et al. NEJM 2015; 373: 834-44[3]	The combination of ambrisentan, a once daily selective endothelin-A–receptor antagonist, and tadalafil, a once daily phosphodiesterase type 5 inhibitor, was the subject of the AMBITION trial (Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension) that evaluated their combined efficacy and safety. AMBITION was an event-driven, double-blind study that included treatment naive patients with WHO Group 1 PAH and WHO Functional class II or III symptoms randomly assigned in a 2:1:1 ratio to receive initial combination therapy with ambrisentan plus tadalafil (combination-therapy group), ambrisentan plus placebo (ambrisentan monotherapy group), or tadalafil plus placebo (tadalafil-monotherapy group), all administered once daily. The primary end point in a time-to-event analysis was the first event of clinical failure, which was defined as the first occurrence of a composite of death, hospitalisation for worsening PAH, disease progression, or unsatisfactory long-term clinical response. Ambrisentan and tadalafil were administered at an increasing dose to a target of 10mg and 40 mg respectively. The primary analysis set (PAS) included 500 participants; 253 were assigned to the combination-therapy group, 126 to the ambrisentan-monotherapy group, and 121 to the tadalafil-monotherapy group. Results: A primary end-point event occurred in 18% of those receiving combination therapy vs 31% of those in the pooled monotherapy group (the two monotherapy groups combined). The hazard ratio (HR) for the primary end point in the combination-therapy group versus the pooled-monotherapy group was 0.50 (95% confidence interval [CI], 0.35 to 0.72; P < 0.001). In essence, the risk of a primary end point event of clinical failure was 50% lower among participants who received initial combination therapy with ambrisentan and tadalafil than among those who received monotherapy with either drug. The treatment effect with respect to the primary end point was driven mainly by a lower rate of hospitalisation for PAH in the combination-therapy group, with combination therapy providing a 63% reduction in the risk of a first PAH-related hospitalisation versus pooled monotherapy (8% of combination therapy patients versus 18% of pooled monotherapy patients (p=0.0002). Hospitalisation for worsening PAH is costly and is associated with a poor prognosis. Additionally, at week 24, the combination-therapy group had greater reductions from baseline in N-terminal pro–brain natriuretic peptide (NTproBNP) levels than did the pooled-monotherapy group (mean change, −67.2% versus −50.4%; P < 0.001), as well as a higher percentage of

		patients with a satisfactory clinical response (39% vs. 29%; odds ratio, 1.56 [95% CI, 1.05 to 2.32]; P = 0.03) and a greater improvement in the 6-minute walk distance (median change from baseline, 48.98 m vs. 23.80 m; P < 0.001). No significant differences with regards to WHO functional class improvements were noted between the treatment groups, with improvements in WHO functional class from baseline ranging from 33-37%. Peripheral oedema, headache, nasal congestion, and anaemia were more common in the combination-therapy group than in either monotherapy group, dizziness was more common in the combination-therapy group than in the tadalafil monotherapy group, and syncope was more common in the tadalafil-monotherapy group than in the other groups; the incidence of hypotension was similar in the three study groups. The rate of discontinuation of a study drug and the rate of serious adverse events (AEs) were similar in the three study groups.[2,4] Conclusion: Among participants with PAH who had not received previous treatment, the risk of the composite outcome of clinical failure was significantly lower among those who received initial combination therapy with ambrisentan and tadalafil than among those who received monotherapy with either ambrisentan or tadalafil treatment alone.
Volibris + tadalafil	Initial combination therapy with ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH): subgroup analysis from the AMBITION trial[10] Coghlan J et al Ann Rheum Dis 2016	This is a post-hoc analysis of patients with CTD-PAH and systemic sclerosis associated PAH (SSc-PAH) from AMBITION (an event-driven double-blind trial in patients with WHO functional class II/III PAH). Patients were randomised 2:1:1 to once daily initial combination therapy with ambrisentan plus tadalafil or monotherapy with ambrisentan or tadalafil respectively. The primary endpoint was time to first clinical failure event (defined as the first occurrence of a composite of death, hospitalisation for worsening PAH, disease progression, or unsatisfactory long-term clinical response). In the primary analysis set (n=500), 187 patients had CTD-PAH, of whom 118 had SSc-PAH. Results: Combination therapy with ambrisentan and tadalafil reduced the risk of clinical failure by 57% vs pooled monotherapy (HR 0.43; 95% CI 0.24 to 0.77). The treatment effect was driven mainly by a lower rate of hospitalisations for PAH in the combination-therapy group with combination therapy providing a 71% reduction in the risk of a first PAH-related hospitalisation versus pooled monotherapy (HR 0.29; 95%CI 0.12 to 0.67). At week 24, greater improvements in NTproBNP and median 6MWD (were also seen +42 vs +24.3m) (statistical significance not reported). The most common adverse event was peripheral oedema which was reported more frequently with initial combination therapy than monotherapy in the PAH-CTD and SSc-PAH subgroups. Importantly, there were no new safety signals observed in this subpopulation although the rates of serious adverse events and adverse events leading to discontinuation of study drug were higher.

		Conclusion: This post-hoc analysis of patients with CTD-PAH from AMBITION suggests that this sub-population did at least as well on initial combination therapy compared with patients with idiopathic/familial PAH both in terms of clinical failure risk reduction and improvement in exercise capacity. In this population, an aggressive treatment approach with initial combination therapy may improve outcomes and exercise capacity versus treatment with monotherapy.
Volibris + tadalafil	Initial combination therapy with ambrisentan and tadalafil and mortality in patients with pulmonary arterial hypertension: a secondary analysis of the results from the randomised, controlled AMBITION study[11] Hoeper M et al Lancet Respir Med 2016; 4: 894-901	An analysis of survival data from the modified intention-to-treat population (n=605) of the AMBITION trial (a multicentre, randomised, double blind study in which treatment naive patients with PAH were randomly assigned in a 2:1:1 ratio to receive combination therapy with ambrisentan and tadalafil, ambrisentan plus placebo or tadalafil plus placebo). Death was rarely recorded as the first 'event of clinical failure' in AMBITION, due to disease progression preceding death, therefore the number of patients who died throughout the study was higher than reported in the primary endpoint. Analysis of the primary endpoint reported deaths is consequently imprecise in determining mortality benefits of the different treatment arms. Two mortality analyses of the AMBITION data were undertaken: (i) A pre-specified analysis was performed of all mortality events from randomisation to the end of the study (including patients who discontinued their assigned treatment); and (ii) a post-hoc analysis assessed survival at 7 days after cessation of a patients randomly assigned treatment (this was based on an analysis undertaken in another event-driven PAH trial, SERAPHIN, to capture events that were more likely to be related to the originally assigned treatment) At the end of the study, survival status was unknown for 15/302 patients in the combination therapy group and 19/303 patients in the pooled monotherapy group. Results: <u>End of Study Analysis:</u> At the end of the study, 29/302 (10%) patients in the combination therapy group had died compared with 41/303 (14%) patients in the pooled monotherapy groups (HR 0.67, 95% CI 0.42-1.08; log rank p=0.10, not significant), indicating that all cause mortality at the end of the study was not significantly different between patients receiving monotherapy and patients receiving initial combination therapy. <u>Randomisation to 7 days after the end of patients assigned treatment (post-hoc):</u> From randomisation to 7 days after the end of a patient's assigned treatment, 3/302 (1%) patients in the combination therapy group had died compared with 13/303 (4%) patients in the pooled monotherapy group (HR 0.21, 95% CI 0.06-0.73; p=0.0065) reflecting a significant risk reduction in all cause

		mortality in those receiving initial combination therapy compared with patients receiving initial monotherapy. Conclusion: Results suggest that initial combination therapy with ambrisentan and tadalafil in treatment-naive patients with PAH might be associated with better long-term survival than initial monotherapy alone.
Volibris + tadalafil	Randomised study of adding tadalafil to existing ambrisentan in pulmonary arterial hypertension[12] Zhuang Y et al Hypertension Research 2014; 37(507-512)	The effects of adding tadalafil to patients stabilised on existing treatment with ambrisentan were investigated in a study by Zhuang et al. This prospective, double-blind, randomised controlled study enrolled 124 patients aged 18–70 years with symptomatic PAH receiving ambrisentan (10mg per day) for 4 months or more. All patients had a diagnosis of idiopathic/familial PAH or PAH related to anorexigen use, connective tissue disease or repaired congenital heart disease. Patients were randomised to treatment with blinded tadalafil 40mg (QD) or placebo for 16 weeks and differences in 6MWD, FC, clinical worsening and adverse events were assessed. Results: Patients receiving combination therapy showed a significantly improved exercise capacity as assessed by the 6MWD and a reduced incidence of clinical worsening events versus those receiving ambrisentan monotherapy alone (both $p<0.05$). No significant differences were found in functional class changes and haemodynamic parameters between the combination and monotherapy groups. No significant differences between groups in treatment emergent adverse events or the overall incidence of adverse events were observed. Conclusion: Tadalafil 40mg daily appears to be well tolerated when added to background ambrisentan. Combined therapy significantly improved exercise capacity and clinical worsening although no significant differences in haemodynamic parameters were observed.
Volibris + tadalafil	Comparison between initial combination therapy and initial monotherapy in pulmonary arterial hypertension: A single centre blinded evaluation of patients enrolled	Haemodynamic changes after 6 months of therapy were assessed in 30 patients enrolled in the AMBITION study from a single centre. Results: At 6 months significant improvements in mean pulmonary arterial pressure, cardiac index, pulmonary vascular resistance and mixed venous oxygen saturation were noted in those receiving combination therapy versus the pooled monotherapy groups (all $p<0.05$), however no significant differences in right atrial pressure were detected[1]. Conclusion: Initial combination therapy is associated with larger improvements in haemodynamics as compared with monotherapy in patients with PAH.

	in the AMBITION study (abstract)[13] Bachetti C et al Am J Respir Crit Care Med, 191;2015:A4779	
Volibris + tadalafil	A comparison of initial combination therapy (ambrisentan and tadalafil) vs monotherapy in FC II vs FC III PAH patients: A subgroup analysis from the AMBITION study (abstract)[14] Frost A et al Am J Respir Crit Care Med 191;2015:A4781	A subgroup analysis of results from the AMBITION trial comparing the efficacy and safety of initial combination therapy in FC II versus FC III PAH subjects from the AMBITION study. These subgroup analyses included the primary endpoint (time to clinical failure) and secondary endpoints from the primary analysis set (PAS). Results: In the overall PAS population, the risk of the primary end point of the first event of clinical failure was 50% lower among participants who received initial combination therapy with ambrisentan and tadalafil than among those who received monotherapy with either drug. The results of this sub-analysis revealed a 79% reduction in clinical failure events (p=0.0052) in FC II patients and a 42% (p=0.0062) reduction in clinical failure events in FC III patients for combination versus pooled monotherapy groups. There was a statistically significant treatment interaction between therapy and functional class with regards to time to clinical failure, with FC II subjects deriving greater benefit than FC III subjects. In a post-hoc analysis of time to first PAH-related hospitalisation, there were no hospitalisations for worsening PAH in the combination therapy group in FC II subjects compared with 14% receiving pooled monotherapy. The mean increase in 6MWD in FC II subjects was smaller compared to FC III subjects with combination therapy (p-value not reported). The safety profile was similar, except for headache which occurred more frequently on combination therapy in FC II versus FC III patients. Conclusion: This subgroup analysis demonstrated that initial combination therapy with ambrisentan and tadalafil significantly reduced the incidence of clinical failure events in both FC II and III subjects, driven largely by a lower rate of hospitalisations. This effect was particularly apparent in FC II subjects.
Flolan + bosentan	BREATHE-2 Combination of bosentan with	Double-blind, placebo-controlled prospective study in which 33 patients with severe PAH (NYHA FC III or IV) started epoprostenol treatment and were randomised for 16 weeks in a 2:1 ratio to receive either bosentan (62.5 mg bd for 4 weeks then 125 mg bd) or placebo.

	epoprostenol in pulmonary arterial hypertension: BREATHE-2[15] Humbert M et al Eur Respir J 2004; 24: 353–359	The primary endpoint was change from baseline to week 16 in total pulmonary resistance (TPR) (a significant fall in TPR of 30% relative to baseline value has been reported to be predictive of improved survival after 3 months of epoprostenol therapy in PPH patients). Secondary endpoints included change in cardiac index (CI), pulmonary vascular resistance (PVR), mean pulmonary artery pressure (mPAP), and mean right atrial pressure (mRAP). Additional secondary endpoints also included 6MWD, the dyspnoea-fatigue rating and modified NYHA functional class of PAH. Results: TPR decreased from baseline to week 16 in both the bosentan/epoprostenol and the placebo/epoprostenol groups. The decrease in TPR was greater in the bosentan/epoprostenol group (-36.3±4.3%) than in the placebo/epoprostenol group (-22.6±6.2%), although the treatment group difference was not statistically significant (p=0.08). Other haemodynamic parameters (CI, PVR, mPAP, and mRAP) improved from baseline in both treatment groups and there were non-significant trends in favour of the bosentan/epoprostenol group. Functional class improved from baseline to week 16 for 13 patients (59%) in the bosentan/epoprostenol group and for five patients (45%) in the placebo/epoprostenol group. The treatment group difference was not statistically significant. Both treatment groups attained clinically relevant increases in the 6MWD (68 m (median) in the bosentan/epoprostenol group versus 74 m (median) in the placebo/epoprostenol group). The median dyspnoea fatigue ratings improved by 1.0 unit in the placebo/epoprostenol group and did not change in the bosentan/epoprostenol group. The treatment group differences for the walk test and dyspnoea-fatigue ratings were not statistically significant. The most frequently reported adverse events were those known to be associated with epoprostenol therapy (jaw pain, diarrhoea, flushing, and headache). Except for diarrhoea, these adverse events were more frequent in the placebo/epoprostenol group. The only adverse event associated with bosentan therapy that occurred more frequently in patients treated with bosentan/epoprostenol than in those on epoprostenol alone was leg oedema (27% versus 9%). Conclusion: The combination of bosentan and epoprostenol therapies may be a therapeutic option for the management of patients with severe pulmonary arterial hypertension.
Flolan + sildenafil	PACES Addition of sildenafil to long-term	A 16-week, double-blind, placebo-controlled, parallel group study to investigate the effect of adding oral sildenafil to long-term IV epoprostenol therapy in patients with PAH. 267 patients with pulmonary arterial hypertension (idiopathic, associated anorexigen use or connective tissue disease, or corrected congenital heart disease) who were receiving long-term intravenous epoprostenol therapy were included.

	intravenous epoprostenol therapy in patients with pulmonary arterial hypertension[16] Simonneau G et al Ann Intern Med. 2008; 149: 521-530.	Patients were randomly assigned to receive placebo or sildenafil, 20 mg three times daily, titrated to 40 mg and 80 mg three times daily, as tolerated, at 4-week intervals. Of 265 patients who received treatment, 256 (97%) patients (123 in the placebo group and 133 in the sildenafil group) completed the study. Primary endpoint was change from baseline in exercise capacity measured by 6MWD. Secondary endpoints included: haemodynamic measurements, time to clinical worsening, and Borg dyspnoea score. Results: A placebo-adjusted increase of 28.8 meters (95% CI, 13.9 to 43.8 meters) in 6MWD occurred in patients in the epoprostenol-sildenafil group which was statistically significant (p<0.001); these improvements were most prominent among patients with baseline distances of 325 meters or more. Relative to epoprostenol monotherapy, addition of sildenafil resulted in a greater change in mean pulmonary arterial pressure by -3.8 mm Hg (CI, -5.6 to -2.1 mm Hg); cardiac output by 0.9 L/min (CI, 0.5 to 1.2 L/min); and longer time to clinical worsening, with a smaller proportion of patients experiencing a worsening event in the epoprostenol-sildenafil group (8 patients) than in the epoprostenol monotherapy group (24 patients) by week 16 (*p* =0.002). There was no effect on the Borg dyspnoea score. Of the side effects generally associated with sildenafil treatment, the most commonly reported in the epoprostenol monotherapy and epoprostenol-sildenafil groups, respectively, were: headache (34% and 57%), dyspepsia (2% and 16%), pain in extremity (18% and 25%), and nausea (18% and 25%). Conclusion: Sildenafil may be used in combination with epoprostenol as part of a multiple treatment regimen to improve exercise capacity in patients with pulmonary arterial hypertension without an apparent increase in adverse events, especially in stable patients with pulmonary arterial hypertension who remain symptomatic despite long-term intravenous epoprostenol treatment.
Flolan + bosentan + sildenafil	Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study[17] Sitbon O et al Eur Respir J 2014; 43: 1691–	A pilot study in which the efficacy and safety of triple combination therapy in patients with severe PAH was investigated. Data from newly diagnosed NYHA FC III/IV PAH patients (n=19) initiated on upfront triple combination therapy with intravenous epoprostenol, bosentan and sildenafil were collected retrospectively from a prospective registry. Patients meeting the inclusion criteria were enrolled between December 2007 and July 2012. The observational period ended in July 2013, 1 year after enrolment of the final patient. Adult patients (18–65 years of age) with idiopathic, heritable or anorexigen-

	1697	associated PAH in NYHA FC III/IV and with severe haemodynamic impairment were eligible for triple combination therapy and included in the study. Bosentan was started concomitantly with epoprostenol therapy at a dose of 62.5 mg twice daily. After 4 weeks, this was increased to 125 mg twice daily for the remainder of the study. Sildenafil was started on study day 5, at the end of the first epoprostenol titration period. Sildenafil was initiated and maintained at a dose of 20 mg three times daily. Variables assessed at baseline, 4 months after initiation of triple combination therapy and once each year until the study end included NYHA FC, 6MWD and pulmonary haemodynamics (assessed by right heart catheterisation (RHC)). Results: Significant improvements in 6-min walk distance and haemodynamics were observed after 4 months' triple combination therapy in 18 patients ($p<0.01$); 17 patients had improved to NYHA FC I or II. One patient was not included in the month 4 assessment (due to an emergency lung transplant in month 3). At the final evaluation (mean±SD 32±19 months), all 18 patients had sustained clinical and haemodynamic improvement. All patients initiated with upfront triple combination therapy were still alive after a mean follow up of 41.2±13.4 months. Most adverse events were typical of epoprostenol therapy (jaw pain, manageable headache, diarrhoea or flushing). Two patients experienced asymptomatic liver enzyme elevation (more than eight times the upper limit of normal), needing bosentan withdrawal after 11.5 and 31.5 months on triple combination therapy. Conclusion: This pilot study provides preliminary evidence of the long-term benefits of upfront triple combination therapy in patients with severe PAH.

5. ***Following ToR 1-4, consider reviewing the cost-effectiveness of existing PBS listings for PAH medicines, and in treatment of WHO functional class II and combination treatment in class III and class IV patients.***

The data in the February 2015 DUSC report indicated that PAH medicines have been used within the PBS restrictions and therefore in a cost-effective manner. It was noted however that there is some discordance between PBS criteria and clinical guidelines in regards to treatment of FC II patients, and use of combination therapy. The PBAC has corroborated that the cost-effectiveness of these indications would require a submission to the PBAC.

The first attempt to request PBS-subsidy for combination therapy was sought by the application for selexipag (Uptravi®, Actelion), which was rejected at the March 2016 PBAC meeting. In contrast to the restrictions for all currently listed PAH agents in which patients are only eligible for one PBS-subsidised PAH agent at any time, the proposed restriction for selexipag specified that it must be used in combination with other PBS-subsidised PAH drugs (an ERA and/or a PDE-5 inhibitor).

Selexipag was intended to be used as 'add-on therapy in patients stabilised on background therapy with an ERA and/or a PDE-5 inhibitor but who had not achieved physician-directed treatment targets.'

The PSD states that the PBAC did not recommend the listing of selexipag on the PBS for PAH as the magnitude of clinical benefit was unclear and the estimate of cost-effectiveness as presented in the submission was difficult to interpret. The submission presented a trial-based cost-effectiveness analysis, in which the incremental effectiveness was measured in terms of the reduction in the number of first morbidity/mortality (MM) events per person-year over the duration of the trial i.e. the incremental cost-effectiveness ratio (ICER) was the incremental cost per unit reduction in the number of first MM events per person-year. It was considered that the ICER presented in the submission was high, especially in the context of an outcome of unclear clinical importance (MM events avoided). The PBAC suggested that the appropriate place in therapy for selexipag was likely to be third line – that is, after patients have tried ERAs and PDE-5 inhibitors as monotherapy and combination. The PBAC acknowledged the difficulty in assessing the cost-effectiveness of selexipag as add-on to combination therapy in the context of combination therapy being broadly accepted as best clinical practice but not currently being subsidised under the PBS. A resubmission for selexipag was tabled at the March 2017 PBAC meeting.

As indicated in the response to ToR-4, the AMBITION study addresses a pivotal clinical question regarding the use of upfront combination therapy in PAH and the study by Zhuang et al provides reassurance of the effectiveness of sequential combination therapy; both studies evaluating ambrisentan plus tadalafil. These data may be beneficial in supporting the cost-effectiveness of this combination treatment.

International cost-effectiveness analyses are referenced in Table 3. It is important to note however that some of these analyses were published prior to the introduction of ambrisentan. In general, it is difficult to draw any robust comparisons or parallels with the Australian system, as product listings, indications, dosages and prices are market specific, each jurisdiction offers its own unique range of treatment options, and accessibility to combination therapy is also quite variable.

Table 3: International cost-effectiveness analyses

Reference	Description
Coyle K, Coyle D, Blouin J et al. Cost effectiveness of first-line oral therapies for pulmonary arterial hypertension: a modelling study. PharmacoEconomics 2016; 34: 509-520	Canadian cost-utility analysis
Canadian agency for drugs and technologies in health (CADTH). CADTH therapeutic review report – drugs for pulmonary arterial hypertension: comparative efficacy, safety, and cost-effectiveness. March 2015	CADTH Therapeutic Review
Chen Y-F, Jowett S, Barton P et al. Clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxsentan and sildenafil for pulmonary arterial hypertension within their licensed indications: a systematic review and economic evaluation. Health Technology Assessment 2009; 13 (49)	NICE HTA *Note that ambrisentan was not licensed at the time in the UK when this HTA was undertaken.*
Stevenson MD, Macdonald FC, Langley J et al. The cost-effectiveness of bosentan in the United Kingdom for patients with pulmonary arterial hypertension of WHO functional class III. Value in Health 2009;12(8):1100- 1105.	UK cost-utility analysis
Roman A, Barbera JA, Escribano P et al. Cost effectiveness of prostacyclins in pulmonary arterial hypertension. Appl Health Econ Health Policy 2012;10(3):175-180.	Spanish cost-utility analysis
Highland KB, Strange C, Mazur J et al. Treatment of pulmonary arterial hypertension. Chest 2003;124(6):2087-2092.	US cost-utility analysis *Note that ambrisentan was not licensed at the time in the US.*
Garin MC, Clark L, Chumney ECG et al. Cost-utility of treatments for pulmonary arterial hypertension. Clin Drug Investig 2009;29(10):635-646.	US cost-utility analysis

Einarson TR, Granton JT, Vicente C et al. Cost-effectiveness of treprostinil versus epoprostenol in patients with pulmonary arterial hypertension: A Canadian analysis. Can Respir J 2005;12(8):419-425.	Canadian cost-minimization analysis
Wlodarczyk JH, Cleland LG, Keogh AM et al. Public funding of bosentan for the treatment of pulmonary artery hypertension in Australia. Pharmacoeconomics 2006;24(9):903-915.	Australian cost-effectiveness analysis (cost per life-year saved)
Narine L, Hague LK, Walker JH et al. Cost-minimization analysis of treprostinil vs. epoprostenol as an alternate to oral therapy non-responders for the treatment of pulmonary arterial hypertension. Current Medical Research and Opinion 2005;21(12):2007-2016.	US cost-minimization analysis
Dranitsaris G and Mehta S. Oral therapies for the treatment of pulmonary arterial hypertension. A population-based cost-minimization analysis. Appl Health Econ Policy 2009;7(1):43-59.	Canadian cost-minimization analysis

Conclusion

As a Sponsor of two important PAH medicines, GSK welcomes participation and stakeholder input into this PMR.

With the evolution of the treatment algorithm in PAH and advances in treatment options, GSK agrees that the scope of the current review is suitable with particular focus given to combination therapy.

We acknowledge the concerns discussed by DUSC and appreciate the need to work with the PBAC and the Government to ensure that PAH patients are treated appropriately and in alignment with current clinical guidelines and best practice.

GSK also remains committed to ensuring comprehensive educational support is provided to Australian healthcare professionals to ensure appropriate use of its medicines.

In consideration that PAH is a highly complex and specialised disease with medicines administered under Section 100 of the *National Health Act* (Highly Specialised Drugs Program) and access restricted to Medicare approved designated centres and written authority approval, GSK recommends a stakeholder forum be held in line with the framework provision of 'significant public interest, complex reviews, or large scale reviews'.

Thank you for your consideration of this input.

References:

1. Galie N et al. 'Updated treatment algorithm of pulmonary arterial hypertension'. JACC 2013; 62:D60-72.

2. Galie N et al. '2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension'. European Heart Journal 2015; doi:10.1093/eurheartj/ehv317.

3. Galie N et al. 'Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension'. NEJM 2015; 373: 834-44.

4. Approved Volibris Product Information

5. Approved Flolan Product Information

6. McLaughlin V et al 'Treatment Goals of Pulmonary Hypertension' JACC 2013; 62 (25):D73-D81

7. Preston I et al 'New perspectives in long-term outcomes in clinical trials of pulmonary arterial hypertension' Eur Resp Rev 2013; 22: 495-502

8. McLaughlin V et al 'End Points and Clinical Trial Design in Pulmonary Arterial Hypertension' JACC 2009; 54 (1): S97-S107

9. Galie N, Simonneau G 'The Fifth World Symposium on Pulmonary Hypertension' JACC 2013; 62(25): D1-3

10. Coghlan J et al 'Initial combination therapy with ambrisentan and tadalafil in connective disease-associated pulmonary arterial hypertension (CTD-PAH): subgroup analysis from the AMBITION trial' Ann Rheum Dis 2016; 0: 1-9

11. Hoeper M et al 'Initial combination therapy with ambrisentan and tadalafil and mortality in patients with pulmonary arterial hypertension: a secondary analysis of the results from the randomised, controlled AMBITION study' Lancet Respir Med 2016; 4: 894-901

12. Zhuang Y et al 'Randomized study of adding tadalafil to existing ambrisentan in pulmonary arterial hypertension' Hypertension Research 2014; 37(507-512)

13. Bachetti C et al 'Comparison Between Initial Combination Therapy and Initial Monotherapy in Pulmonary Arterial Hypertension: A Single Centre Blinded Evaluation of Patients Enrolled in the AMBITION Study' Am J Respir Crit Care Med, 191;2015:A4779 (abstract)

14. Frost A et al 'A Comparison of Initial Combination Therapy (ambrisentan and tadalafil) vs monotherapy in Functional Class (FC) II vs FC III PAH Patients A Subgroup Analysis from the AMBITION Study' Am J Respir Crit Care Med 191;2015:A4781 (abstract)

15. Humbert M et al 'Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2' Eur Respir J 2004; 24: 353–359

16. Simonneau G et al 'Addition of Sildenafil to Long-Term Intravenous Epoprostenol Therapy in Patients with Pulmonary Arterial Hypertension' Ann Intern Med. 2008; 149: 521-530

17. Sitbon O et al 'Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study' Eur Respir J 2014; 43: 1691–1697