Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ambrisentan

Proprietary Product Name: Volibris

Sponsor: GlaxoSmithKline Australia Pty Ltd

July 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
6MWD	6 minute walk distance
ACPM	Advisory Committee on Prescription Medicines
AE	adverse event
APAH	associated pulmonary arterial hypertension
AUC	area under the plasma drug concentration-time curve
BDI	Borg dyspnoea index
Cmax	maximum serum concentration of drug
CMI	Consumer Medicine Information
EoS	End of Study
ERS	European Respiratory Society
ESC	European Society of Cardiology
FC	Functional Class
GSK	GlaxoSmithKline
HPAH	heritable pulmonary arterial hypertension
IPAH	idiopathic pulmonary arterial hypertension
ITT	intention to treat
LV	left ventricular
mITT	modified intention to treat
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PAH	pulmonary arterial hypertension
PD	pharmacodynamic(s)
PI	Product Information
PK	pharmacokinetic(s)
PVR	pulmonary vascular resistance
RMP	Risk Management Plan

Abbreviation	Meaning
SAE	serious adverse event
SF-36	Short form 36 (health survey)
TEAE	treatment emergent adverse event
Tmax	time taken to reach the maximum concentration (Cmax)
Vd	volume of distribution
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	9 February 2016
Date of entry onto ARTG	16 February 2016
Active ingredient:	Ambrisentan
Product name:	Volibris
Sponsor's name and address:	GlaxoSmithKline Australia Pty Ltd Level 3, 436 Johnston Street Abbotsford VIC 3067
Dose form:	Tablets
Strengths:	5 mg and 10 mg
Container:	Blister pack
Pack sizes:	10 and 30 tablets
Approved therapeutic use:	Volibris in combination with tadalafil is indicated for the treatment of WHO Group 1 pulmonary arterial hypertension (PAH) in patients with WHO functional class II, III or IV symptoms.
Route of administration:	Oral
Dosage:	5 mg once daily. Additional benefit may be obtained by increasing the dose to 10 mg.
ARTG numbers:	143739, 143743

Product background

This AusPAR describes the application by GlaxoSmithKline Australia Pty Ltd (GSK) to extend the indications for ambrisentan (trade name: Volibris) to include combination therapy with tadalafil for the treatment of pulmonary arterial hypertension (PAH). Volibris is a selective endothelin receptor antagonist.

The current indications are:

Ambrisentan:

Volibris is indicated for the treatment of:

- *Idiopathic pulmonary arterial hypertension (PAH)*

- *Pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD),*

in patients with WHO functional class II, III or IV symptoms.

Tadalafil:

Adcirca is indicated in adults for the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.

The proposed indications are:

Volibris, as monotherapy is indicated for the treatment of:

- *Idiopathic pulmonary arterial hypertension (PAH)*

Pulmonary arterial hypertension associated with:

- *connective tissue disease (PAH-CTD)*

in patients with WHO functional class II, III or IV symptoms.

Volibris is indicated for the treatment of pulmonary arterial hypertension (PAH and PAH-CTD in combination with tadalafil to reduce the risk of clinical failure (a composite of death, PAH hospitalisation, disease progression, and unsatisfactory clinical response) and to increase satisfactory clinical response and exercise ability

GSK is not the sponsor of Adcirca and there is no proposed change to the tadalafil indication with this submission.

The current dosage is:

Ambrisentan:

Volibris should be taken orally at a dose of 5 mg once daily. Additional benefit may be obtained by increasing the dose to 10 mg.

Tadalafil:

The recommended dose is 40 mg (2 x 20 mg tablets) taken once daily with or without food.

The proposed dosage is:

Volibris as a single agent:

- Volibris should be taken orally at a dose of 5 mg once daily. Additional benefit may be obtained by increasing the dose to 10 mg.

Volibris used with tadalafil:

- When used in combination with tadalafil the Volibris dose should be titrated to 10 mg once daily (*see Clinical Trials*).

Pulmonary artery hypertension (PAH)

- Pulmonary hypertension is characterised by elevations in mean pulmonary arterial pressure (mPAP) (≥ 25 mmHg at rest). These haemodynamic changes result in impairment of right ventricular function and may lead right heart failure and death.
- The WHO classification of pulmonary hypertension is based on aetiology and mechanism and is divided into 5 groups. Group 1 is pulmonary arterial hypertension (PAH) and consists of sporadic idiopathic PAH (IPAH), heritable PAH (HPAH) and associated PAH (APAH) due to disease affecting small pulmonary arterioles (drugs and

toxins, connective tissue diseases, HIV infection, portal hypertension, congenital heart disease [excluding congenital inflow and outflow tract obstruction and congenital cardiomyopathies] and sickle cell disease)

- Without treatment the median survival is approximately 2.8 years. There is no curative medication, and no combination of medications has been shown to prevent disease progression in the long term.
- There are a number of registered treatments in Australia for PAH including inhaled epoprostenol, inhaled iloprost, oral bosentan, oral ambrisentan, oral sildenafil, and oral macitentan, in addition to oral ambrisentan and oral tadalafil.

Ambrisentan

- Ambrisentan was designated an Orphan Drug for the treatment of patients with PAH to improve exercise capacity, delay clinical worsening and decrease the symptoms of PAH in July 2007.
- Ambrisentan is a non-sulfonamide propanoic acid; a relatively selective endothelin type A (ETA) receptor antagonist. Inhibition of ETA inhibits phospholipase C-mediated vasoconstriction and protein kinase C-mediated cell proliferation, while preserving nitric oxide and prostacyclin production, cyclic GMP and cyclic AMP-mediated vasodilation and endothelin-1 (ET-1) clearance associated with endothelin type B (ETB) receptors.
- Ambrisentan is rapidly absorbed, about 98.8% plasma protein bound, primarily (96.5%) to albumin. It displays linear kinetics. Almost half the absorbed dose is excreted unchanged and the remainder is glucuronidated or metabolised by CYP3A4 (and to a lesser extent CYP3A5 and CYP2C19). Two thirds of the unchanged ambrisentan and its metabolites are eliminated in the bile and the remainder is renally eliminated. The plasma half-life is 13.6 to 16.5 h. Steady state is usually achieved after 4 days of repeated dosing.
- Ambrisentan is currently approved for the following indication:

  Volibris is indicated for the treatment of:

  - *Idiopathic pulmonary arterial hypertension (PAH)*
  - *Pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD),*

  in patients with WHO functional class II, III or IV symptoms.
- Ambrisentan has been previously considered by ACPM/ADEC, as a new chemical entity in 2008.

Tadalafil

- Tadalafil is a reversible inhibitor of cyclic GMP (cGMP) specific phosphodiesterase type 5 (PDE5i). This addresses the impaired release of nitric oxide by the vascular endothelium associated with PAH and consequent reduction of cGMP concentrations within the pulmonary vasculature. Increase cGMP results in relaxation of the pulmonary vascular smooth muscle and vasodilation of the pulmonary vascular bed. Tadalafil is rapidly absorbed and has a mean Cmax of 4 h. Absolute bioavailability has not been determined. The Vd is 77 L at steady state. Tadalafil is 94% plasma protein bound but this was not affected by impaired renal function. It is mainly metabolised by CYP3A4. The major circulating metabolite is not clinically active. The mean terminal half-life is 16 h. Tadalafil is excreted as an inactive metabolite (61% in faeces, and 36%

in the urine). It exhibits linear kinetics over the dose range. In pop Pk modelling steady state 40 mg doses was 26% higher in patients versus healthy volunteers. Clearance is reduced in the elderly with a half-life of 22 h and a 25% greater exposure after 10 mg dosing. In patients with mild and moderate renal impairment tadalafil exposure doubled. Haemodialysis did not contribute to tadalafil elimination. Mild to moderate hepatic impairment did not affect tadalafil exposure. Tadalafil exposure was 19% lower in diabetics.

- It was granted orphan designation for the treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise ability in April 2010.
- It was approved for the following indication in August 2011:

  Adcirca is indicated in adults for the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.

Ambrisentan in combination with tadalafil

- Extensions of the indications for ambrisentan to include the use of tadalafil have been approved in the EU and the US. Different approaches have been taken to the amendments of the wording of the indications:

  US

  Letairis is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group1):

  - *To improve exercise ability and delay clinical worsening*
  - *In combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability*

  EU

  Volibris is indicated for treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, including use in combination treatment (see section 5.1). Efficacy has been shown in idiopathic PAH and in PAH associated with connective tissue disease.

The TGA adopted EU guidelines of relevance for this submission, in additional to the general guidance documents were:

- EMEA/CHMP/EWP/356954/2008: Guidelines on the Clinical Investigations of Medicinal Products for the Treatment of Pulmonary Arterial Hypertension; and
- CHMP/EWP/83561/2005: Guideline on Clinical Trials in Small Populations (effective December 2006).

Regulatory status

The international regulatory status at the time of this submission to TGA is listed in Table 1.

Table 1: International regulatory status of Volibris at time of submission to TGA.

Country / region	Submission date	Status	Indications (approved or requested)
EU (centralised procedure)	9 Dec 2014	CHMP: positive opinion received on 27 Oct 2015 EU: Commission Decision estimated by end of Dec 2015	Volibris is indicated for treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, including use in combination treatment (see section 5.1). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.
US	5 Dec 2014	Approved: 2 Oct 2015	Letairis is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1): - To improve exercise ability and delay clinical worsening. - In combination with tadalafil to reduce the risks of disease progression and hospitalisation for worsening PAH, and to improve exercise ability. Studies establishing effectiveness included trials predominantly in patients with WHO Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).
Canada	27 Feb 2015	Ongoing	
Switzerland	9 Jan 2015	Ongoing	
Russia	27 Feb 2015	Ongoing	
Brazil	25 May 2015	Ongoing	

Country / region	Submission date	Status	Indications (approved or requested)
Japan	Clinical study report submitted to the PMDA on 25 Dec 2014 In Japan, GSK received approval of Ambrisentan with PAH indication on 23 Jul 2010. PMDA confirmed that the current approved PAH indication is applicable for both monotherapy and combination therapy. Therefore, GSK can promote combination therapy in Japan.		

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Ambrisentan is a selective endothelin receptor type A (ET_A) antagonist.

Tadalafil is an orally active selective inhibitor of the enzyme PDE-5, the primary cyclic guanosine monophosphate hydrolysing enzyme in smooth muscle.

There are both clinical and nonclinical data to support the combination therapy of ambrisentan with tadalafil. In an animal model, the combined use of ambrisentan and tadalafil had a synergistic effect on pulmonary hypertension in rat pulmonary arteries.[1] There were no clinically significant PK interaction between ambrisentan and tadalafil in a study in healthy volunteers. In two small clinical studies in patients with PAH, beneficial effects were observed when tadalafil was added to existing ambrisentan[2] and when ambrisentan was added to tadalafil.[3]

The main therapies currently used for PAH target the signalling pathways in PAH. These include the prostacyclin derivatives which target the cyclic adenosine monophosphate dependent prostacyclin pathway; the phosphodiesterase type-5 inhibitors which target the cyclic guanosine monophosphate dependent nitric oxide pathway, and the endothelin receptor antagonists which target the phospholipase-C-dependent endothelin pathway. Other medications currently used for PAH include diuretics, anticoagulants and calcium channel blockers. Although the evolution of treatments for PAH has lengthened survival time, improved exercise tolerance, hemodynamics, and quality of life for patients with PAH, it remains a life threatening illness. The mean 3 year survival is around 67%.

The sponsor's rationale for this submission is to expand the therapeutic indications for ambrisentan to include combination therapy with tadalafil. This is on the basis of clinical trial evidence showing benefits of combined therapy.

> *Evaluator's comments: Both ambrisentan and tadalafil are on the ARTG for the treatment of pulmonary hypertension. There are no barriers to physicians using these two medications as combination therapy.*
>
> *This application for an extension of indications for use of a medicine in combination with another medicine, but without a new fixed dose combination or combination pack is unusual. Many drugs such as those for diabetes and hypertension are used in combination, but the combined use as such is not specifically stipulated in the indication section of the PI. A number of other drug combinations have been studied for the treatment of PAH, most of these have been small clinical trials. The CPMP/EWP guidelines for the approval of fixed dose combination medicines are applicable to this application. However, unlike a fixed dose combination medicine, an extension of indication to include two tablets does not have the benefits of ease of administration and potential cost saving that a once daily tablet would have.*

Guidance

Three guidance documents:

[1] Liang F, et al. Ambrisentan and tadalafil synergistically relax endothelin-induced contraction of rat pulmonary arteries. *Hypertension* 59: 705-11 (2012).
[2] Oudiz R, et al. ATHENA-1. Hemodynamic improvements following the addition of ambrisentan to background PDE5i therapy in patients with pulmonary arterial hypertension. *Chest* 140: 905A (2011); Shapiro S, et al. ATHENA-1. Long term clinical improvement following the addition of ambrisentan to background PDE5i therapy in patients with pulmonary arterial hypertension. *The Journal of Heart and Lung Transplantation* 31: No 4S (2012).
[3] Zhuang Y, et al. Randomised study of adding tadalafil to existing ambrisentan in pulmonary arterial hypertension. *Hypertension Research* 37: 507-512 (2014).

- CPMP/ICH/36396: Statistical Principles for Clinical Trials;
- EMEA/CHMP/EWP/356954/2008: Guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension; and
- CPMP/EWP/240/95: Guideline on the clinical development of fixed combination medicinal products.

Paediatric data

The submission did not include paediatric data. The sponsor has submitted a European Paediatric Investigation Plan; the due date of the first report is February 2014. There is no American paediatric plan as this is not required for orphan drugs. There is a small paediatric population with PAH. The priority in any drug development program for children is to assess the pharmacokinetics, define a safe and efficacious dose, and provide an appropriate formulation.

Good clinical practice

An AUDIT certificate is included in the dossier to verify that the pivotal AMBITION study was conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with the International Conference of Harmonisation Good Clinical Practice guidelines.

Pharmacokinetics

No original studies with pharmacokinetic data were submitted.

Pharmacodynamics

No new pharmacodynamic data was submitted.

Dosage selection for the pivotal studies

The dosage selected for the clinical studies is consistent with the formulations available in Australia, and what is recommended in the individual product's PI.

Efficacy

Studies providing efficacy data

The AMBITION study (Study AMB112565) is a pivotal efficacy and safety study for the use of ambrisentan in combination with tadalafil as initial therapy for PAH. The AMBITION study was a Phase III-IV, randomised, double blind, three arm study which compared initiating treatment for PAH with a combination therapy with ambrisentan and tadalafil, monotherapy with ambrisentan or monotherapy with tadalafil. The main efficacy outcome was clinical failure defined as either death, hospitalisation for worsening of PAH, disease progression or unsatisfactory long term clinical response. All patients were to receive at least 24 weeks of treatment. The subjects continued in the study until a clinical failure event occurred, or after data freeze (when the target number of primary endpoints was reached). The study was conducted in 120 centres in 14 countries. It was co-sponsored by GSK and Gilead Sciences. The first subject visit was 18 October 2010; the last was 31 July 2014.

Ambrisentan added to tadalafil for PAH

The sponsor did not submit any other clinical studies for evaluation but referred to two abstracts in relation to this indication. A commentary is provided in the Extract Clinical Evaluation Report accompanying this AusPAR.

Evaluator's conclusions on efficacy

The AMBITION study investigated patients with Type 1 PAH and WHO functional class II and III. The study reported combination therapy had a positive effect on a pooled primary efficacy endpoint defined as 'time to clinical failure'. This was largely due to a reduction in hospitalisation for PAH. There was no significant impact on death rate, although the study was not powered to assess this. Of the secondary efficacy endpoints, there was a statistically significant effect on 6MWD and NT-proBNP. There was no significant improvement in WHO classification scores or quality of life scores.

ANCOVA and subgroup analysis demonstrated those patients with WHO subgroup II and those with younger age responded better to both combined therapy and each monotherapy.

While the study demonstrated a benefit of combination therapy for the composite primary endpoint there were a number of study design issues that limited its ability to address other relevant clinical outcomes. These were:

- The long dose titration therapy resulted in less than 24 weeks at the specified target dose. A longer duration of therapy or follow up would have improved the ability to evaluate a significant effect on mortality.
- The primary analysis compared combination treatment with pooled monotherapy. Although this may increase the power and sensitivity to find a positive result it may also create bias if one monotherapy arm was better than the other. In addition, what is clinically relevant is if combination therapy in treatment naïve patients is better than the current treatment of monotherapy with add on combination therapy for patients who did not improve.
- The design of the study having an end point of first 'clinical failure event' limits the ability of the trial to find a potential benefit in ongoing 'clinical failure' events or long term mortality. Pooling clinical failure events reduces the power of the study to detect significant changes in individual components. The individual components of the clinical failure event score are examining very different parameters and one cannot extrapolate a benefit from a pooled score to individual components of the score.
- The question the clinician would want to know is if a patient is better started with ambrisentan and stepped up to add tadalafil if there is no improvement, or to use ambrisentan in combination with tadalafil at the onset. This study does not answer this question, as patients who deteriorated or did not achieve the desired improvement with ambrisentan monotherapy were classified as a clinical failure event. This would bias the results towards finding a positive benefit in the combination therapy group.

In the pivotal clinical trials for ambrisentan for PAH (ARIES I and ARIES II), treatment with ambrisentan for 12 weeks resulted in significant improvements in 6MWD (around 30m), BDI, WHO functional class, time to clinical worsening and SF-36 health survey physical functional scale. In long term follow up studies, improvements in 6MWD were sustained and Kaplan-Meier estimates of survival at 1, 2 and 3 years were 93%, 85%, and 79%.

In the pivotal clinical trials for tadalafil (Adcirca), there was a statistically significant dose dependent improvement in 6MWD after 16 weeks of treatment. The mean change in 6MWD in the group treated with 40 mg was 44m. This was accompanied by a statistically

significant improvement in quality of life as measured by the SF36. However, there was no significant change in WHO functional class, episodes of clinical worsening or BDI.

Unlike ARIES and ADCIRCA, in the AMBITION study, the improvement in 6MWD was not associated with an improvement in WHO classification or quality of life.

Not including patients with WHO class IV excluded a subgroup of patients with more severe disease who may have benefitted from early combination therapy.

Safety

Studies providing safety data

The following safety data were collected:

- General adverse events (AEs) were assessed by the investigators. Adverse events were coded using MedDRA version 16. Only treatment emergent adverse events were recorded (defined as those events that started on the day of or after IP initiation, and up to 30 days after the last dose).
- Adverse events of special interest (AESI) included liver events, anaemia, hypersensitivity, hypotension and fluid retention.
- Laboratory tests, including those for biochemistry, testicular function and haematology were assessed at each study visit.
- ECG was performed at baseline, Week 24 and FAV.

Patient exposure

Patient exposure in the mITT population to the end of study was on average 603 days in the combination therapy group, 500 days in the ambrisentan monotherapy group and 542 days in the tadalafil monotherapy group. A total of 88 patients were exposed to an additional mean of 400 days of combination therapy.

Post marketing data

No data submitted.

Evaluator's conclusions on safety

The safety profile described is as expected on the basis of the known safety profile of ambrisentan and tadalafil. Although overall there were similar proportions of subjects with AEs among the three treatment groups, the investigator attributed more adverse events in the combination therapy group to be due to the study drugs. AEs were the major cause of withdrawal from the study. As is the case with many chronic diseases, it can be difficult to differentiate the adverse events from the disease versus those of the treatment.

The most common AE with combination therapy was peripheral oedema. Headache, flushing, nasal congestion, vomiting and rash were more commonly seen with combination therapy than with either therapy alone. Liver related abnormal events were infrequent and no more common with combination therapy. There was a greater likelihood of anaemia with combination therapy and ambrisentan; this may have been driven by peripheral vasodilatation and volume overload. There was a greater fall in diastolic blood pressure in the combination therapy group.

First round benefit-risk assessment

First round assessment of benefits

The benefits of the use of ambrisentan in combination with tadalafil as initial therapy for grade II-III PAH versus pooled monotherapy with either ambrisentan or tadalafil are:

- A 50% risk reduction in clinical failure event, (predominately less hospitalisation for PAH)
- An improvement in 6MWD. The mean overall improvement with combination therapy was approximately 49m, or approximately 24m better than the pooled monotherapy group

Notably, there was no statistically significant reduction in deaths or disease progression; however the study was not powered to examine this. There were no significant improvements in WHO classification, BDI or qualitative health measures. This raises questions about the clinical significance of the positive results.

Subgroup analysis demonstrated that younger patients and those with WHO functional class II were more likely to respond to combination therapy.

The potential benefits are supported by evidence of a pharmacodynamic effect in an animal model and improvement of a surrogate marker NT-pro-BNP.

First round assessment of risks

The risks of using ambrisentan in combination with tadalafil for PAH as proposed:

- Increased incidence of adverse events attributed to the study medication- in particular peripheral oedema, headache, anaemia, rash and fall in diastolic blood pressure
- Potential for use in groups where the risks and benefits of therapy were not studied (for example, grade IV PAH) and in groups where the risk of side effects was higher

There is also the risk of accepting the results of the AMBITION study as evidence that combination therapy with ambrisentan and tadalafil as initial therapy as superior to individual monotherapy when the study design was not adequate to address this question. The clinical evaluator is concerned that the monotherapy arms do not reflect current clinical practice, as a real patient with PAH who has inadequate response to one therapy would have treatment optimised with another agent or a prostanoid.

First round assessment of benefit-risk balance

The prognosis in untreated PAH is poor. The median survival time of untreated patients is 2.8 years. The CHMP guidelines state that therapy for PAH should be efficacious for clinically significant endpoints such as mortality and morbidity.

The use of ambrisentan in combination with tadalafil had a statistically significant benefit in the outcome 'time to clinical failure'. This was primarily driven by less hospitalisation. There were also statistically significant improvements in 6MWD (but questionable clinical significance) and clinical endpoints at 24 weeks. However, there was no reduction in mortality or improvement in efficacy outcomes such as WHO classification or qualitative health outcomes.

Other studies of combination therapy with ambrisentan and tadalafil as add on therapy have also shown positive haemodynamic responses and changes in NT-pro-BNP.[4] Clinical

[4] Oudiz R, et al. ATHENA-1. Hemodynamic improvements following the addition of ambrisentan to background PDE5i therapy in patients with pulmonary arterial hypertension. *Chest* 140: 905A (2011); Zhuang Y, et al.

outcomes were more significant after treatment for 48 months.[5] However, these studies were small and underpowered.

Although this submission is not for a fixed dose formulation, the issues surrounding the approval of the use of two medications in combination are similar. According to the guidelines for fixed dose combinations, to extend the indication of ambrisentan for use in combination with tadalafil, the sponsor needs to provide evidence of either:

- a) An improvement in the benefit/risk ratio due to
  - 1. Addition or potentiation of therapeutic activities of the substances which results in:
    - i. A level of efficacy similar to the one achievable by each active substance used alone at higher doses than in combination, but associated with a better safety profile

    OR
    - ii. A level of efficacy above the one achievable by a single substance with an acceptable safety profile
  - 2. Counteracting an adverse effect
- b) Simplification of therapy.

and that there is robust evidence for efficacy in this indication.

Category (a.1.ii) best suits this application, as the safety profile demonstrates more adverse effects attributable to the study drugs with combination therapy than individual monotherapy. Although there was an impressive reduction in clinical failure events in the AMBITION study, the clinical evaluator is not convinced of the clinical significance of this due to the lack of efficacy on death rate and quality of life.

Treatment for patients with PAH is generally co-ordinated by a physician with expertise in this area. Although there are no nationally adopted guidelines for management, for patients with type 1 PAH, monotherapy with either a PGE-5i or ET antagonist is recommended as initial therapy, with combination therapy reserved for those who do not respond to one agent and combination therapy or prostanoids for those who remain symptomatic.[6] There are currently no restrictions on physicians choosing a number of different combination therapies for their patients.

First round recommendation regarding authorisation

The sponsor has submitted the results of a pivotal clinical trial of ambrisentan in combination with tadalafil for the management of treatment naïve patients with PAH. At this stage, the clinical evaluator would not recommend approval of the proposed extension of indication for ambrisentan in combination with tadalafil as initial therapy for patients with PAH for the following reasons:

- The level of evidence for efficacy from the AMBITION study is not strong enough to support a new indication.

Randomised study of adding tadalafil to existing ambrisentan in pulmonary arterial hypertension. *Hypertension Research* 37: 507-512 (2014).

[5] Shapiro S, et al. ATHENA-1. Long term clinical improvement following the addition of ambrisentan to background PDE5i therapy in patients with pulmonary arterial hypertension. *The Journal of Heart and Lung Transplantation* 31: No 4S (2012).

[6] Anderson JR, Nawarskas JJ. Pharmacotherapeutic management of pulmonary arterial hypertension. *Cardiol Rev.* 18: 148-62 (2010).

The improvement in clinical failure event was statistically significant, but the significance of this for clinical practice is uncertain. The positive efficacy endpoint was driven by less hospitalisation, but the reason for hospitalisation is not given. There was no significant difference in death rates, disease progression, unsatisfactory clinical response or quality of life between combination therapy and ambrisentan monotherapy. As standard clinical practice would be to add-on therapy for those who failed monotherapy, a better comparator would have been to include an add-on therapy arm. The improvement in 6MWD between the combination therapy group and monotherapy group was 24m, which was less than what is considered clinically significant and not associated with an improvement in BDI, WHO functional class or patient quality of life.

The indications proposed do not specify if combination therapy is to be used as initial therapy or add on therapy, accurately reflect the patient population of the AMBITION study or accurately state the positive clinical efficacy endpoints.

However, the sponsor has submitted a pivotal trial for the use of combination therapy with ambrisentan and tadalafil. The clinical evaluator would approve the addition of this information to the clinical trials and adverse events sections of the PI, after some clarification about the design of the trial and suggested amendments to the PI.

It is important to note that the current indications for ambrisentan are sufficient to allow clinicians to use ambrisentan in combination with tadalafil for patients with PAH if this is considered clinically appropriate.

Clinical questions

Efficacy

1. Provide clarification how patient events were coded after an initial failure event. For example, if a patient was hospitalised and then discharged, would further events also be coded in the trial? Were some events given more weight than others?
2. The provision of a justification for the use of pooled analysis of monotherapy for the primary efficacy outcome rather than comparison with ambrisentan monotherapy.
3. An explanation as to why patients with WHO stage IV were not included in the study.
4. An explanation as to whether the high dropout rate affected the power of the study.
5. Provision of further information concerning the reason for hospitalisations for PAH. For example: What were the indications for hospitalisation? Were the admissions initiated by patient or physician? What treatment was received?

Safety

6. Provide an explanation for a difference in the number of patients who discontinued treatment with the IP versus those who withdrew from the study and how these events were defined taking into account if the discontinuation of treatment was a decision of the subject or treating doctor or investigator.
7. An explanation as to why in the combination therapy group there was a mean weight loss of the group taking into account that these patients were also more likely to develop fluid overload. Was there any assessment of lean body mass?
8. The provision of any information available as to whether the abnormalities in liver function were reversible or not.

Other

9. The provision of clarification if the concerns with dose uniformity of the tablets described in the EU also apply to the formulation used in Australia. If so, were there plans to update the Australian PI.
10. A request to provide further information in relation to the Paediatric development Plan and the use of ambrisentan in children.

Second round evaluation

Details of sponsor's responses to clinical questions and evaluator's subsequent comments are contained in Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

The AMBITION study demonstrated a clinically and statistically significant improvement in time to clinical failure with the combination of ambrisentan and tadalafil in patients with untreated grade II-III PAH.

The sponsor's responses to the questions and comments in relation to the evaluator's comments did not result in any factual changes in the data but assisted in the interpretation of the data. The evaluator was more informed about the acceptability of composite end points for efficacy in this population and of the clinical relevance of the outcomes measured. Most of the concerns of the study design were addressed.

The evaluator provides indications of an awareness of the difficulties in designing studies of rare diseases, particularly when the outcome events of interest are poorly defined and may occur years after diagnosis. The evidence for efficacy in the AMBITION study was not considered to be as robust as in the SEREPHIN study but does suggest a benefit for the primary, some of the secondary and the surrogate endpoints.[7]

Second round assessment of risks

The risks were assessed as unchanged as a result of the data presented. The risks of combination therapy are those expected from the use of the individual components. The risks are adequately described in the PI.

Second round assessment of benefit-risk balance

After consideration of the sponsor's responses to the evaluator's clinical questions and concerns about the efficacy end points, the risk balance ratio for the use of ambrisentan in combination with tadalafil as initial therapy for stage II-III PAH is favourable.

Although there is some evidence of a benefit in using both ambrisentan and tadalafil as initial therapy for patients with stage II-III PAH, it is unknown how this combination compares with the use of Ambrisentan and other PGE-5i (as is recommended in the PAH guidelines).

[7] The sponsor states that the composite endpoints in AMBITION included all those within the SERAPHIN composite endpoint plus two additional measures: hospitalisation for PAH, and unsatisfactory long-term clinical response. AMBITION was a treatment strategy trial of upfront combination versus monotherapy with already established, efficacious PAH treatments.

Second round recommendation regarding authorisation

The clinical evaluator recommends approval of the extension of indication for the use of ambrisentan in combination with tadalafil as initial therapy for stage II-III PAH on the condition that the sponsor amends the indications in the PI to state:

> *Volibris can be used with tadalafil as initial treatment of WHO stage II and III PAH.*

This restricts the use of combination therapy to better reflect the study population in the clinical trial. There is insufficient evidence for the safety or efficacy of combination therapy in patients with stage IV-PAH.

Alternatively, the sponsor could chose not to amend the indications and vary the register with changes to the clinical trials, adverse events and dosing sections of the PI only. This is not to understate the benefits that the AMBITION study demonstrated. But it is the evaluator's opinion that the latter option allows clinicians a wider scope in the use of ambrisentan as more research and changes in clinical practice emerge.

V. Pharmacovigilance findings

TGA granted a waiver from the requirement for a Risk Management Plan (RMP) for this application.

VI. Summary and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

No new quality data were submitted.

Nonclinical

No new nonclinical data were submitted.

Clinical

The clinical evaluator has recommended approval for the amended indication:

> *Volibris can be used with tadalafil as initial treatment of WHO stage II and III PAH and no LV risk factors.*

The evaluator was of the view that there was insufficient evidence for the safety or efficacy of combination therapy in patients with WHO functional class IV disease.

Pharmacology

No new pharmacology data were provided. The pharmacology of ambrisentan and tadalafil have been summarised in the background to this submission.

The co-administration of ambrisentan with tadalafil in healthy volunteers has been previously studied. The concomitant administration of a single dose of ambrisentan had no clinically relevant effect on the pharmacokinetics of either ambrisentan or its metabolite, 4 hydroxymethyl ambrisentan. The single dose pharmacokinetics of tadalafil (40 mg) were unaffected by multiple doses of ambrisentan (10 mg once daily).

Efficacy

AMBITION study

This was a Phase III-IV, randomised, double blind, event driven, three arm study comparing initial treatment with either combination therapy with ambrisentan and tadalafil, ambrisentan monotherapy (and tadalafil placebo), or tadalafil monotherapy (and ambrisentan placebo) in 605 adult (aged 18-75 years) patients with WHO Class 1 PAH, Functional class II and III. Other inclusion criteria were weight >40 kg, total lung capacity > 60% predicted, FEV1 > 50% predicted, negative VQ scan, an ability to walk 125-500 m, resting SaO2 ≥ 88% with or without supplemental oxygen, and stable HIV disease(if HIV positive). Exclusion criteria were numerous but included patients with portopulmonary and pulmonary veno-occlusive disease and patients with 3 or more left ventricular disease risk factors (BMI > 30 kg/m^2, essential hypertension, diabetes mellitus and a history of significant coronary disease), significant anaemia, fluid retention or rare retinal diseases (non arteritic anterior ischaemic optic neuropathy or hereditary degenerative retinal disorder). Exclusion on the basis of heart failure risk factors was not part of the initial protocol but was introduced as a protocol amendment more than one year after the commencement of the study. Patients with 3 or more risks factors were included prior to the protocol change. These patients continued in the study and the results were included in analyses of the whole ITT population and were analysed separately as the non modified intention to treat (non mITT) patient group. Patients with ≤ 2 risk factors were analysed as the mITT patient group.

The sample size was based on an overall event rate of 15% and HR of 0.47, but this was revised after 2 years because of a lower than expected event rate (12% per year). A sample size of 614 patients (520 mITT subjects) was estimated to be required to obtain 105 mITT subjects with a first event, giving a 97% power for the comparison of combination therapy and pooled monotherapy and 85% power for the comparison of combination therapy and each monotherapy group.

The ambrisentan monotherapy group started at a dose of 5 mg daily titrated to 10 mg daily if tolerated over 8 weeks. The tadalafil group started at 20 mg and titrated up to 40 mg over 4 weeks. The combination therapy of ambrisentan and tadalafil commenced at 5 mg and 20 mg with titration to 10 mg and 40 mg, respectively.

The study continued until there had been at least 105 adjudicated first clinical failure events and each patient had completed at least 24 weeks of therapy. Patients were encouraged to stay in the study after a clinical failure event. The investigator could continue the same therapy, change to blinded combination therapy (presumably single blind therapy), or initiate prostanoids. After the 105 events all patients were notified to return for a final assessment visit (FAV) within 28 days or their Week 24 visit, whichever was later. The patients continued to receive their blinded treatment until the last patient had complete their FAV, after which all returned for an EoS visit within 4 weeks. EoS events were not used in the primary analysis.

A total of 605 patients received investigational product. Of those, 500 had ≤ 2 heart failure risk factors (mITT) and 105 had ≥ 3 heart failure risk factors (non-mITT). In the mITT population, the mean age was 54 years (23 to 74 years) and females comprised 74% of the combination therapy group, 79% of the ambrisentan monotherapy group and 83% of the tadalafil monotherapy group. Approximately half were post-menopausal. Overall, 53% had IPAH, 44% APAH and 3% HPAH. Between 66 and 70% patients had a WHO FC score of III. The baseline BDI overall was 3.5-4. It was slightly higher in the tadalafil monotherapy group and the pro-BNP was slightly lower, but the baseline 6 MWD was similar between groups (mean 357 m). The mITT group had the following distribution of heart failure risk factors - 40% had hypertension, 10% had diabetes mellitus, and 4% had coronary artery disease. The non-mITT population was older (mean age 62.8 years), overall 70% female,

64% WHO FC III, with a mean 6MWD of 330.5 m and a BDI score of 4. About 77% had hypertension, 56% had diabetes mellitus, and 21% had coronary artery disease. Across the whole study, only 2% of patients had prior PAH therapy. Baseline haemodynamic parameters were similar across the treatment groups in both ITT populations. The non-mITT population had an overall higher mean PCWP but lower mean mPAP and PVRI than the mITT population.

Important protocol deviations occurred in 17% of patients across the study. In the mITT population these were mostly eligibility criteria deviations (predominantly pulmonary function test criteria not met) and in the non-mITT population deviations of PAH diagnosis or class or haemodynamic criteria after the major protocol amendment).

Overall, 78% of the mITT population and 60% of the non-mITT population completed the study. In the mITT population, during dose titration 8%/3%/2% of the combination/ambrisentan/tadalafil groups, respectively, discontinued because of adverse events. By the end of the study, 17%/24%/23% of the combination/ambrisentan/tadalafil groups in the mITT population, and 31%/35%/43% of the combination/ambrisentan/tadalafil groups in the non-mITT population discontinued, mostly because of adverse effects

The mean duration of randomised therapy was 466.5 to 550 days in the mITT population and 466.1 and 557.3 in the non-mITT population. After a clinical failure event the investigator could elect to not change treatment, change to blinded combination therapy or change to prostanoids. Of those that changed therapy in the mITT population 83 patients received blinded ambrisentan and tadalafil for proximately 367 days, 5 received ambrisentan monotherapy (for a mean of approximately 56 days) and one received tadalafil monotherapy (for 14 days).

The primary outcome was the difference between first line combination therapy and the pooled results for first line monotherapy with either ambrisentan or tadalafil for the time to the first clinical failure event. This was defined as:

- Death (all cause),
- Hospitalisation for worsening PAH (any worsening of PAH, admission for lung/heart/lung transplant, atrial septostomy or initiation of parenteral prostanoid therapy),
- Disease progression (> 15% decrease from baseline in 6MWD combined with WHO class III or IV symptoms), or
- Unsatisfactory long-term clinical criteria (received >1 dose of randomised treatment and in the study for ≥ 6 months AND decreased from baseline in 6MWD at 2 consecutive post baseline clinic visits separated by ≥ 14 days AND WHO class III symptoms assessed at 2 clinic visits separated by ≥ 6 months).

Outcomes were measured at the final assessment visit (FAV). This assessment occurred either 28 days from the projected 105th adjudicated first clinical failure event in the mITT population of at the Week 24 visit (whichever was later).

The primary outcome for the mITT population is included in Table 2. Comparisons were also provided for the individual monotherapy groups.

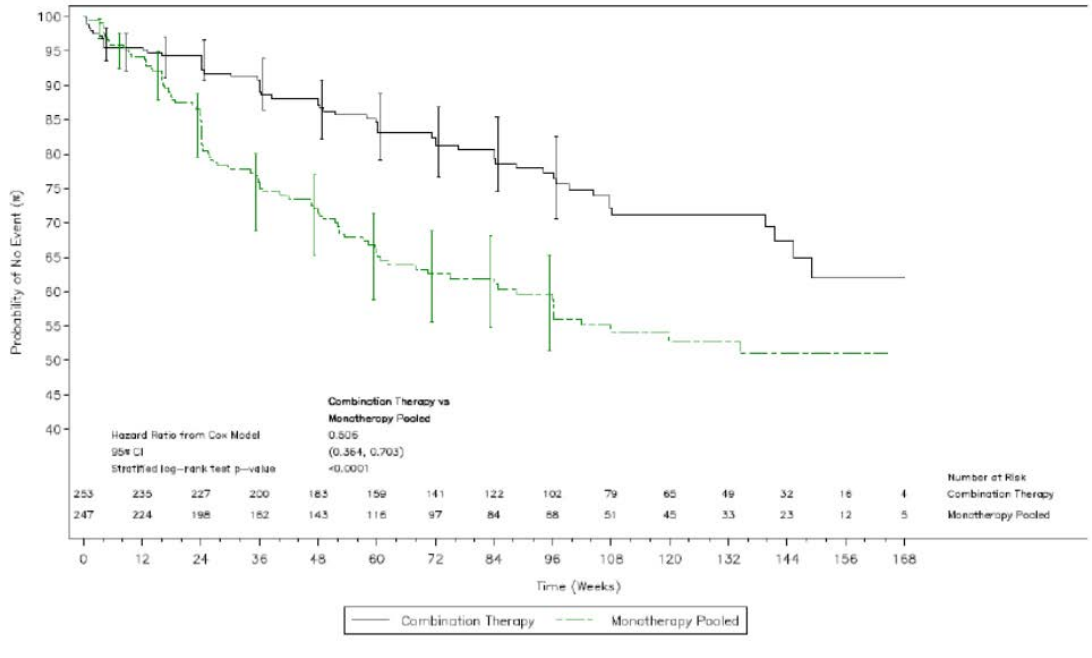
Table 2: Time to first adjudicated clinical failure event in the mITT population.

	Combination Therapy N=253		Monotherapy Pooled N=247		Ambrisentan Monotherapy N=126		Tadalafil Monotherapy N=121		Total N=500	
Subjects with Event	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
First Clinical Failure Event	46	(18)	77	(31)	43	(34)	34	(28)	123	(25)
Death (all-cause)	9	(4)	8	(3)	2	(2)	6	(5)	17	(3)
Hospitalization for worsening PAH	10	(4)	30	(12)	18	(14)	12	(10)	40	(8)
Any hospitalization for worsening PAH	6	(2)	21	(9)	12	(10)	9	(7)	27	(5)
Initiation of parenteral prostanoid therapy	4	(2)	9	(4)	6	(5)	3	(2)	13	(3)
Lung or heart/lung transplant	0		0		0		0		0	
Atrial septostomy	0		0		0		0		0	
Disease progression	10	(4)	16	(6)	12	(10)	4	(3)	26	(5)
Unsatisfactory long-term clinical response	17	(7)	23	(9)	11	(9)	12	(10)	40	(8)
Analysis of time to first clinical failure event	n	(%)	n	(%)	n	(%)	n	(%)		
Number of subjects censored	207	(82)	170	(69)	83	(66)	87	(72)		
Kaplan-Meier probability of event by 1 yr (%)	11.09		24.47		24.04		24.87			
95% CI	(7.62, 16.01)		(19.28, 30.76)		(17.12, 33.13)		(17.71, 34.27)			
Kaplan-Meier probability of event by 2 yrs (%)	20.28		36.77		38.84		34.34			
95% CI	(15.07, 27.00)		(30.07, 44.42)		(29.66, 49.69)		(25.22, 45.60)			
Kaplan-Meier probability of event by 3 yrs (%)	32.41		43.89		47.85		39.39			
95% CI	(23.23, 44.03)		(35.57, 53.21)		(36.77, 60.34)		(27.53, 54.09)			
Hazard Ratio from Cox Model			0.502		0.477		0.528			
95% CI			(0.348, 0.724)		(0.314, 0.723)		(0.338, 0.827)			
Stratified log-rank test p-value			0.0002		0.0004		0.0045			
Proportional Hazards assumption p-value			0.9489		0.7595		0.8951			

Source: m2.7.3, Table 3-7

Notes: Table is based on a subject's first event. Hazard ratio from the Cox Proportional Hazards model and stratified log-rank p-value adjusted for Etiology of PAH (IPAH/HPAH vs. Non-IPAH) and WHO Functional Class (II vs. III). For censored subjects, time (days) is calculated as the number of days from randomization to final assessment visit. Comparisons are for combination therapy relative to monotherapy pooled, ambrisentan monotherapy or tadalafil monotherapy.

Figure 1: Kaplan Meier Curve for time to first investigator assessed clinical failure event (baseline to FAV) in the mITT population.



Note: 95% confidence intervals (using log-log transform method) are presented for each treatment group at weeks 4, 8, 16, 24, then every 12 weeks up to week 96.

The KM probability of events over three years predicts the initial benefit of the combination therapy over monotherapy for the primary outcome may decline with time.

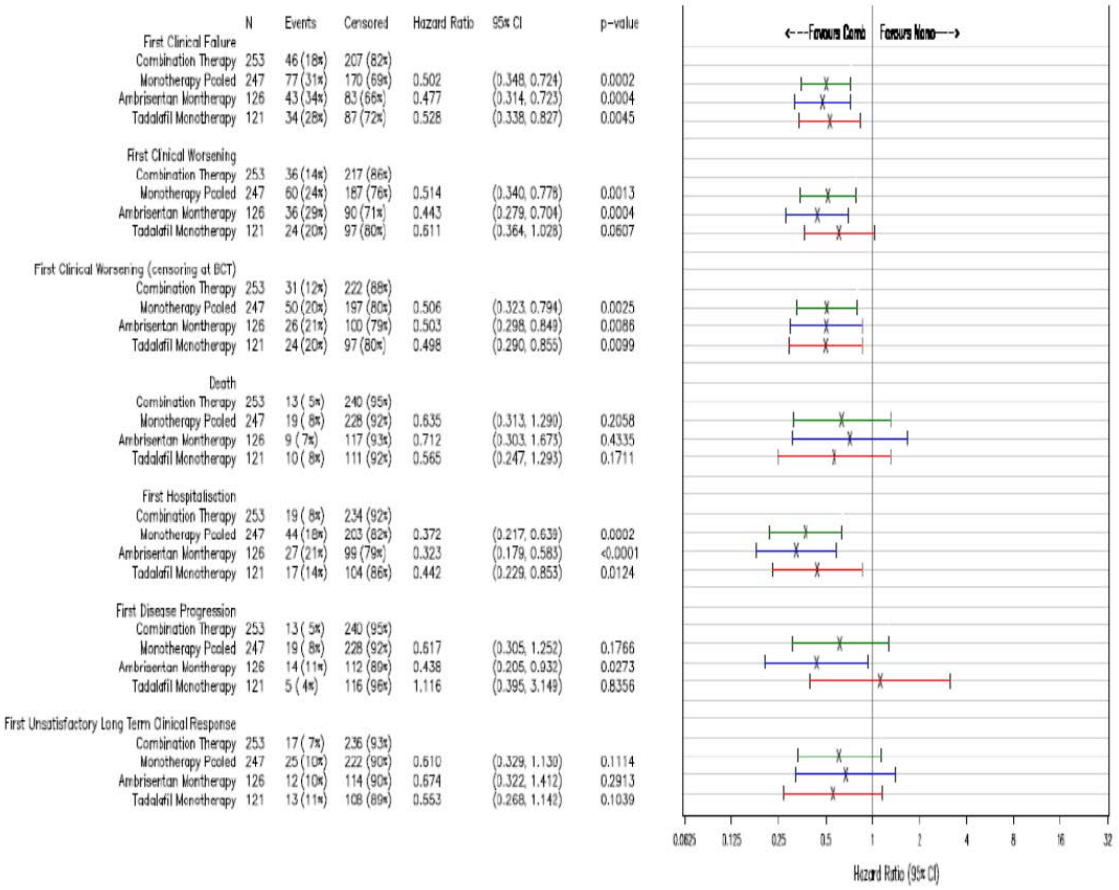
Event numbers were driven by hospitalisation for worsening PAH, and to a lesser extent the number of patients requiring prostanoids, and disease progression. The small numbers of events limit the analysis of the components of the primary endpoint.

First clinical failure events in the non-mITT population were reported in 29%/38%/38%/37% of the combination/pooled monotherapy/ambrisentan monotherapy/tadalafil monotherapy groups respectively.

A sensitivity analysis was conducted for the time to first clinical worsening defined as death, hospitalisation for worsening of PAH and disease progression. A first clinical worsening event occurred in 10% fewer patients (a 49% decrease in events) between the combination therapy group and the pooled monotherapy group in the mITT population (HR 0.51, 95% CI 0.34-0.78, p = 0.0013). The results were driven by a reduction in hospitalisation for worsening PAH. Within the pooled monotherapy groups, clinical worsening outcomes were more common in the ambrisentan group (17%) (HR 0.443, 95% CI 0.28-0.7, p = 0.004) than the tadalafil group (12%) (HR 0.61, 95% CI 0.36-1.03, p = 0.06). The KM estimates of event probability were more favourable for the combination therapy than the pooled monotherapy or the individual therapies. In the non-mITT population the first clinical worsening events were reported in 22%/36%/38%/33% of the combination/pooled monotherapy/ambrisentan monotherapy/tadalafil monotherapy groups respectively.

The forest plot, Figure 2 below, depicts the measured outcomes of first clinical failure event, first clinical worsening and the individual components of these endpoints and compares pooled monotherapy and the individual monotherapies with combination therapy.

Figure 2: Forest plot of first adjudicated endpoints in the mITT population.



Note: Adjusted hazard ratio > 1 indicates a higher risk for Combination therapy compared with monotherapy group.
Hazard ratio from the Cox Proportional Hazards model and stratified log-rank p-value adjusted for Aetiology of PAH (IPAH/HPAH vs Non-IPAH) and WHO functional class (II vs III).

Comparing baseline to the end of the study (4 weeks after the final assessment visit) similar differences were found between the combination therapy, pooled and individual

monotherapy groups as were seen in the FAV analyses. The HRs for combination therapy compared with pooled monotherapy/ambrisentan monotherapy/tadalafil monotherapy for the time to clinical failure event were 0.54 (95% CI: 0.41, 0.72)/0.51(95% CI: 0.37,0.71)/0.57 (95% CI: 0.41, 0.79), respectively.

The quantitative secondary outcomes were:

- Change from baseline at Week 24 in N-terminal pro-B type natriuretic peptide(NT-pro-BNP)
- % subjects with satisfactory clinical response at Week 24
- Change from baseline at Week 24 in 6MWD
- Change from baseline at Week 24 in WHO functional Class
- Change from baseline at Week 24 in BDI

The change from baseline of NT-pro-BNP at Week 24 in the combination therapy group compared with the monotherapy group and the individual monotherapies are as shown in Table 3.

Table 3: NT-Pro BNP natriuretic peptide (ng/L) at Week 24 in the mITT population.

	Combination Therapy N=253	Monotherapy Pooled N=247	Ambrisentan Monotherapy N=126	Tadalafil Monotherapy N=121
Baseline, n	236	235	120	115
Mean (CV)	1601.1 (3.84)	1498.7 (3.34)	1557.0 (3.53)	1437.9 (3.14)
Min – Max	21 – 11289	36 - 28135	41 – 7787	36 - 28135
Week 24, n	214	205	102	103
Mean (CV)	539.2 (3.15)	1033.4 (3.79)	822.6 (3.78)	1242.1 (3.80)
Min – Max	18 - 7289	16 - 37144	16 - 11238	16 - 37144

A satisfactory clinical response (defined as ≥ 10% improvement in 6MWD compared to baseline, improvement to or maintenance of WHO Class I or II symptoms, and no events of clinical worsening prior to or at week 24) compared with baseline was found for the combination therapy versus the pooled (HR 1.56 (1.05, 2.32), p = 0.026) and tadalafil (1.72 (1.05, 2.83), p=0.32) monotherapy groups but not ambrisentan (1.42 (0.88, 2.31), p = 0.15). There were modest increases in 6MWD in all groups but the median difference from baseline was statistically significantly greater for the combination (median 49 m) than either the pooled monotherapy (median 23.8 m)or the ambrisentan (median 24.8 m) and tadalafil monotherapy groups (median 20.9 m). Of the patients in the combination therapy group WHO FC III 46% had a documented improvement in functional class, however while 12% improved FC in those patients with WHO FC II baseline. There was no statistically significant difference between the combination and pooled monotherapy groups. Differences between groups were not analysed for statistical significant for the BDI because the preceding test in the testing hierarchy was not statistically significant. The median reduction in score for the combination therapy was -1.00 (IQR 2.00 to 0) in the mITT and -0.5 (IQR -1.5 to 1.0).

The qualitative secondary outcomes were scores for SF-36 and CAMPHOR. Both SF-36 and CAMPHOR scores (sub scores for energy, breathlessness and mood) had a numerical but not statistically significant improvement. As there were other quantitative measurable differences between groups a possible explanation is a lack of specificity in the tool, or the lack of importance in the items measured to the patient.

Ambrisentan added to ongoing tadalafil for PAH

An abstract summarising the findings of an open label efficacy and safety study of 33 WHO FC II subjects with PAH and a suboptimal response to PDE-5i the initial treatment with

ambrisentan was 5 mg daily and increased to 10 mg daily after 4 weeks, and continued for 20 weeks. Haemodynamic improvements were noted for PVR, mPAP and Cardiac Index, 6MWD, BDI and NT-pro BNP. Statistical significance was claimed for the comparisons. A second abstract summarising the findings of the next 24 weeks of the study (to week 48) with patients continuing 10 mg once daily ambrisentan for the additional 24 weeks showed a 96% survival and 80% freedom from clinical worsening and most (97%) improved or maintained their WHO functional class through to 48 weeks. The improvement in 6MWD and BDI noted at the earlier analysis, although similar to the earlier comparison, no longer reached statistical significance.

Tadalafil added to ongoing ambrisentan for PAH

A publication by Zhuang[8] was provided in supportive information. This was a prospective, randomised, double blind study of 124 adults aged ≤ 70 years with PAH stable WHO FC II and III for at least 1 month, who had been receiving ambrisentan for at least 4 months. Prostanoids and other PDE inhibitors were excluded medications but vasodilators, diuretics, anticoagulants, cardiac glycosides and oxygen were permitted. In the 16 week double blind period patients received tadalafil (40 mg daily) (n = 60) or placebo (n = 64) in addition to their existing therapy with ambrisentan (10 mg daily). All haemodynamic parameters improved in the both the combination therapy group and the ambrisentan group during the study but no change was statistically significantly different from ambrisentan alone. At each 4 week measurement, the 6MWD increased for each group. A statistically significant increase from baseline was noted at trial exit between the combination therapy group and the ambrisentan group. A subgroup analysis showed patients ≤ 2 years of PAH, patients with a baseline 6MWD of ≤ 325m and those with baseline WHO FC 1-II showed greatest improvement although statistically significant improvement for combination therapy over ambrisentan alone was shown for the subgroups. Clinical worsening (death, transplantation, arterial septostomy, hospitalisation due to worsening PAH, initiation of new therapy or worsening FC by Week 16) occurred in 8.3% of the combination therapy patients and 21.9% of the ambrisentan patients (p = 0.046). There was a numerical but not statistically significant reduction in the proportion of patients with WHO FC worsening (18.8% versus 8.3%).

Safety

A total of 605 patients were exposed to investigational product and 253 were exposed to combination therapy initially, and a further 88 patients were exposed to the combination after the first clinical failure. In the mITT population the average exposure was 603 days for the combination, 500 days for ambrisentan therapy (n = 126) and 542 days for tadalafil therapy (n = 121). A further 88 patients were exposure for an average of 404.6 days to the combination therapy. In the whole ITT population, 98%/96%/94% of patient son combination therapy/ambrisentan monotherapy/tadalafil monotherapy reported an AE. Patients in the non-mITT population were more likely to experience severe TEAEs than the mITT population. The most common events in the combination therapy group were peripheral oedema (45%), headache (41%) and diarrhoea (21%); similarly in the ambrisentan monotherapy group peripheral oedema (38%), headache (34%), and diarrhoea (22%); and the tadalafil monotherapy group they were peripheral oedema (28%), headache (35%), and dyspnoea (19%). AEs leading to discontinuation of therapy occurred in 12%/11%/12% of the combination ambrisentan, tadalafil groups, respectively in the mITT population, and in the non-mITT population 33%/37%/17%. AEs leading to withdrawal from the study occurred in 9%/7%/11% of the combination/ambrisentan/tadalafil groups, respectively in the mITT population and in

[8] Zhuang Y, et al. Randomised study of adding tadalafil to existing ambrisentan in pulmonary arterial hypertension. *Hypertension Research* 37: 507-512 (2014).

the non-mITT population 20%/27%/13%. The most common AEs leading to discontinuation were dyspnoea, peripheral oedema, and headache in the combination group, pulmonary hypertension, cardiac failure and peripheral oedema in the ambrisentan monotherapy group although the only discontinuations in the tadalafil group were due to myalgia. A similar pattern of AEs were seen in patients withdrawing from the study, although no TEAE was reported to be the cause of patient withdrawals in the tadalafil group. In the mITT population 75%/60%/56% of the combination/ambrisentan/tadalafil groups and in the non-mITT population 71%/69%/63% had AEs reported by the investigator as treatment related. Across the study headache, peripheral oedema, nasal congestion and flushing were the most common.

Deaths in the safety set included those that occurred up to 30 days after the last dose of investigational product. In the mITT populations deaths were reported for 3%/2%/7% of the combination/ambrisentan/tadalafil groups respectively, and in the non-mITT population 2%/12% /7%. Overall there were fewer deaths in the combination therapy group compared with the remainder. The causes of death were consistent with those expected in a population with PAH. In the mITT population, SAEs occurred in 36%/36%/41% of the combination/ambrisentan/tadalafil and in the non-mITT 57%/58%/43%. The most frequent SAEs were pneumonia, pulmonary hypertension anaemia and syncope.

Fluid retention was identified in 55%/40%/36% of the combination/ambrisentan/tadalafil from the mITT population and 61%/69%/47% of the non-mITT population. Peripheral oedema was the most commonly observed event. Hypotension was reported for 32%/27%/27% in the combination/ambrisentan/tadalafil groups in the mITT population and dizziness for 20%/19%/12%. In the non-mITT population hypotension occurred in 24%/38%/43% and dizziness in 12%/23%/27% (that is, fewer reports of both event types with combination therapy in patients with heart failure risk factors). Systolic blood pressure reduction was seen in all therapy groups, and was numerically greatest with combination therapy. The most marked reductions in systolic blood pressure were seen in the non-mITT population and the largest reduction was in the ambrisentan monotherapy groups (mean reduction in systolic and diastolic BP of about 10 mm Hg) at Week 24. Overall, the greatest reductions were in diastolic blood pressure, an in general more marked in the combination therapy groups (both populations). Hypotension is not listed as an adverse effect in the PI. Anaemia was an event of special interest and was reported in 20%/10%/13% of the combination/ambrisentan/tadalafil groups of the mITT population and 24%/19% /17% of the non-mITT population. Hypersensitivity was reported in 13%/10%/7% of combination/ambrisentan/tadalafil groups of the mITT population and 14%/0%/27% of the non-mITT population. The most frequently reported event in this category was rash. In the study protocol AST or ALT > 3x ULN resulted in discontinuation of the investigational product. In the mITT population, 5 patients in the combination therapy group and 2 patients in the tadalafil monotherapy group met this criterion. Two non-mITT patients met the Hy's law laboratory criteria but had other conditions to which the results were attributable. Similar proportions of patients in the ambrisentan and combination therapy groups developed elevated transaminases. About 10% of ambrisentan patients on monotherapy or combination therapy developed clinically significant increases in serum creatinine. Ambrisentan is contraindicated in pregnancy, and the three pregnancies were reported during the study and were terminated.

No post market data were submitted for the combination of ambrisentan and tadalafil.

Risk management plan

TGA granted a waiver from the requirement for an RMP for this application.

Risk-benefit analysis

Delegate's considerations

Efficacy

- Efficacy of the combination of ambrisentan and tadalafil was demonstrated in a single multicentre, double blind, active comparator, event driven study of 500 patients with ≤ 2 risk factor for heart failure and a further 105 with ≥ 3 risk factors for heart failure. The use of time to clinical worsening as an endpoint for study in pulmonary arterial hypertension is consistent with the TGA adopted EU guidelines.[9] There was a significant reduction in clinical failure events in the combination therapy group compared with the ambrisentan monotherapy group. The comparison between the tadalafil monotherapy group and the combination therapy group for this outcome was marginally statistically significant. The driver of the outcome was a reduction in hospitalisations. The sponsor argues hospitalisations are a surrogate for disease progression. Early in the clinical trial there was a protocol change that resulted in the exclusion of patients with multiple risk factors for heart failure from the study population. Analysis of the patients with ≥ 3 heart failure risk factors showed the primary outcome was also positive for the combination of ambrisentan and tadalafil, although the study was not powered for this comparison. Combination therapy resulted in a significantly greater improvement in clinical response 39% than the pooled monotherapy (29%) and the tadalafil component of the monotherapy. Exercise ability was improved more with combination therapy than with monotherapy. All groups showed some improvement with quality of life measures but there was no significant difference between the groups. The most favourable outcomes in the mITT population for the combination compared with the individual monotherapies were for women from North America with WHO FC II. The combination therapy in all the ITT populations showed a benefit over ambrisentan alone.

Safety and RMP

- The most commonly reported AEs in the study populations were headache, fluid retention, gastrointestinal upset (including diarrhoea) and dyspnoea. Anaemia in previous clinical trials with ambrisentan was more frequent with the 10 mg dosing and is listed as a very common AE in the PI based on the long term safety study of ambrisentan alone. Anaemia was commonly reported, and was twice as common in the mITT population with combination therapy, and 1.3 fold more common in the non-mITT population. Hepatic enzyme elevation is a known safety concern for the endothelin receptor antagonist class, and an elevation of liver function tests was included in the protocol of the Ambition study as a trigger for discontinuation. Fluid retention manifest as peripheral oedema was commonly reported across the study, more frequently in patients on combination therapy. Hypotension was reported in the AMBITION study. This events was not reported for ambrisentan previously but has been reported for tadalafil. It occurred in about 30% of patients across the study in combination with tadalafil, but it was also common in the monotherapy groups also. Hypersensitivity reactions, most commonly rash have previously been reported for ambrisentan, and in the Ambition study. Overall, the safety events were consistent with the types of events previously reported for ambrisentan and included in the PI, with the exception of hypotension. The sponsor has not included this AE in the draft PI but has proposed its inclusion.

[9] EMEA/CHMP/EWP/356954/2008: Guidelines on the Clinical Investigations of Medicinal Products for the Treatment of Pulmonary Arterial Hypertension.

Dose

- The doses supported by the studies are similar to those for the current indication. The starting dose was 5 mg, and was to be up-titration to 10 mg daily.

Indication

- On consideration of the patient population in the study the indication for the combination of ambrisentan and tadalafil for WHO class 1 PAH with WHO FC II or III symptoms is supported. The clinical evaluator recommended the addition of 'and no LV risk factors' into the indication. However, the protocol change that excluded patients with multiple risk factors for heart failure occurred after 105 patients with ≥ 3 risk factors had been enrolled. Patients with ≤ 2 risk factors continued to be enrolled, and 40% of the mITT patients had hypertension. Although there is no specific subgroup analysis with patients at risk of heart failure based on risk factors the delegate does not agree that excluding patients with any LV risk factors represents the study population.
- The evidence in the submission supports the use of ambrisentan and tadalafil for the management of pulmonary arterial hypertension. The proposed statement that Volibris in combination with tadalafil is to reduce the risk of clinical failure and to increase satisfactory clinical response and exercise ability represent therapeutic claims that are best included and described in the Clinical Trials Section. The Delegate therefore proposes an amended extension of indication as follows:

  Volibris in combination with tadalafil is indicated for the treatment of WHO class 1 pulmonary artery hypertension in patients with WHO functional class II or III symptoms.

Data deficiencies

- This was a single pivotal study, and although there is one additional publication and two abstracts there is limited detail in the supportive studies. The protocol of the pivotal study was amended and patients at higher risk of adverse events and poorer clinical outcomes were excluded. Consistent with the previous indication for ambrisentan there were no children enrolled.

Conditions of registration

There are no proposed special conditions of registration proposed at this time. Special conditions may be proposed in the post Advisory Committee on Prescription Medicines (ACPM) letter.

Questions for the sponsor

The sponsor is requested to address the following issues in the pre ACPM response:

- The protocol was amended after the commencement of the study to exclude patients with three or more risk factors for heart failure. Please comment on the implications of this change for the integrity of the study, and how these issues were resolved.
- How many patients had one or more left ventricular risk factors in the study? What proportion of patients was in each treatment group? What were the primary outcomes for these patients? How do the primary outcomes compare with patients with no LV risk factors?
- Please comment on the sensitivity of the Borg Dyspnoea score to detect meaningful differences between groups as used in this study.
- Please confirm that the problems with the search functions of the adverse event database that previously resulted in the inadvertent omission of some adverse events from PSURs (correspondence dated 24 October 2012) have been resolved.

Proposed action

The Delegate has no reason to say, at this time, that the application for the product should not be approved for registration.

The Delegate's proposed amended indication is:

> *Volibris is indicated for the treatment of:*
>
> - *Idiopathic pulmonary arterial hypertension (PAH)*
> - *Pulmonary arterial hypertension 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 class 1 pulmonary artery hypertension in patients with WHO functional class II or III symptoms.*

Summary of issues

- Whether, based on a small single pivotal study, there is sufficient evidence to support this indication
- The impact of the change of protocol on the study population and the overall integrity of the study.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

- Can the efficacy outcomes be accepted for all patients with WHO Class 1 PAH given the change of protocol and the resultant exclusion of patients with multiple risk factors for heart failure?
- The study population only enrolled patients with WHO FC class II and III symptoms, although a small number progressed to class IV symptoms. Should patients with class IV symptoms be excluded from the indication?
- Has sufficient evidence been provided to support the combination therapy as second line therapy or, based on the evidence should it be for initial therapy only?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Executive summary

GSK welcomes the TGA's Delegate's assessment that there are no reasons not to register Volibris (ambrisentan) in combination with tadalafil for the treatment of PAH. Volibris is currently indicated for monotherapy of idiopathic PAH and PAH associated connective tissue disease. A submission was made to TGA on 30 January 2015 to extend the indication of Volibris to include combination therapy with tadalafil for the treatment of PAH. The expanded indication is supported by a Phase III-IV randomised, double blind, event driven, three arm clinical study (AMBITION study) comparing initial treatment with combination therapy of ambrisentan and tadalafil, ambrisentan monotherapy (and tadalafil placebo), or tadalafil monotherapy (and ambrisentan placebo) in 605 patients (aged between 18 to 75 years) with WHO Group 1 PAH, with FC II and III symptoms.

The combination therapy of Volibris with tadalafil has received a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) on 22 October 2015. The US Food and Drug Administration approved the combination therapy of Letairis (ambrisentan) with tadalafil on 2 October 2015.

PAH is a life threatening disease with no curative treatment, and GSK believe that PAH affected patients, should have access to the best available new standard-of-care treatment and one that has been appraised and approved by the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Hence, GSK support the combination therapy of Volibris and tadalafil, as first line and second line therapy.

Specific questions raised by the TGA delegate for the ACPM's advice

The ACPM is requested to provide advice on the below specific issues. GSK has provided their position on each of the 3 questions.

- 1. Can the efficacy outcomes be accepted for all patients with WHO Class 1 PAH given the change of protocol and resultant exclusion of patients with multiple risk factors for heart failure?

GSK Position

The efficacy outcomes can be accepted for all patients with WHO Group I PAH given the change of protocol and resultant exclusion of patients with multiple risk factors for left heart disease (diastolic dysfunction). The ITT population (all randomised subjects who received at least one dose of investigational product) efficacy results for the primary and secondary endpoints were consistent with the mITT population (all randomised subjects who received at least one dose of investigational product and met the Protocol Amendment 2 modified inclusion/exclusion criteria) results. Protocol Amendment 2 strengthened hemodynamic inclusion criteria and excluded patients with numerous factors for left heart disease, specifically those with covert diastolic dysfunction. Please refer to response to Sponsor Question 1.

- 2. The study population only enrolled patients with WHO FC II and III symptoms; although a small number progressed to class IV symptoms. Should patients with class IV symptoms be excluded from the indication?

GSK position

GSK recognises that the AMBITION trial only included patients in WHO FC II and III. However, the study by Zhuang,[10] an ambrisentan/tadalafil sequential combination trial, which was provided in the original application, included patients in WHO FC II, III and IV (8.1% FC IV across the treatment arms). In the overall analysis, the study met its primary endpoint of improved 6MWD and clinical worsening after 16 weeks ($P<0.05$ versus placebo). This evidence highlighted the benefits of combination therapy in patients with FC IV symptoms.

The international evidence based PAH treatment guidelines, the ESC/ERS Guidelines 2015 also recommends upfront ambrisentan and tadalafil therapy for WHO FC IV patients, whom as defined by the FC definition, exhibit very limited to no exercise capacity.

On the basis of available data and ESC/ERS recommendations, it is reasonable for the ACPM to consider the inclusion of patients with class IV symptoms in the indication, as this will support health care professionals in providing access to a new standard-of-care treatment for seriously ill patients, and may ensure an improved quality of life.

[10] Zhuang Y, et al. Randomised study of adding tadalafil to existing ambrisentan in pulmonary arterial hypertension. *Hypertension Research* 37: 507-512 (2014).

- 3. Has sufficient evidence been provided to support the combination therapy as second line therapy or, based on the evidence should it be for initial therapy only?

GSK position

The use of combination treatment is the standard of care in the treatment of PAH, following the conclusion of a number of studies showing the benefit of combination treatment. This is reflected in the recently updated ESC/ERS Guidelines 2015 for the diagnosis and treatment of pulmonary hypertension, which recommends the initiation of combination treatment in patients with mild, intermediate and severe PAH.[11] The results of the AMBITION study have recently been published[12] and indicate a clear benefit for patients initiated on a combination of ambrisentan and tadalafil (which is reflected in the ESC/ERS Guidelines where the combination of ambrisentan and tadalafil has the highest class recommendation and level of evidence for initial drug combination therapy).[13]

The Zhuang study[14] evaluated sequential ambrisentan/tadalafil combination. This study was a prospective, double blind, randomised controlled study aimed to investigate the efficacy and safety of tadalafil in patients receiving background ambrisentan therapy. In this study, 124 patients with confirmed PAH, who had received ambrisentan (10 mg daily) for at least 4 months were randomised to receive tadalafil (40 mg daily) or placebo. At week 16, the group which received tadalafil showed a significantly improved exercise capacity as assessed by the 6MWD ($P<0.05$). In addition, 8.3% of patients in this group had clinical worsening versus 23.4% with placebo ($P<0.05$). Consistent with these clinical benefits, patients taking tadalafil also showed improved cardiopulmonary haemodynamics including Pulmonary Artery Pressure (PAP), Pulmonary Vascular Resistance (PVR) and Cardiac Output (CO), although these results were not statistically significant compared with the placebo group. No significant differences were found in adverse events between the placebo and tadalafil groups. Sequential combination therapy of ambrisentan and tadalafil therefore provides a safe and effective therapeutic strategy for patients with WHO FC II-IV PAH.

Questions for the sponsor

1. The protocol was amended after the commencement of the study to exclude patients with three or more risk factors for heart failure. Please comment on the implications for this change for the integrity of the study and how these issues were resolved?

GSK would like to clarify that the amendment was made not to exclude patients with risk factors for (left) heart failure, but rather to ensure that the study recruited patients with WHO Group 1 Pulmonary Hypertension (that is, patients with PAH) and not those from WHO Group 2 (that is, Pulmonary hypertension due to left heart disease).[15] The amendment strengthened hemodynamic inclusion criteria and excluded patients with numerous factors for left heart disease, specifically those with covert diastolic dysfunction.

[11] Galiè N, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 37: 67-119 (2016).
[12] Galiè N, et al. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. *N Engl J Med.* 373: 834-44 (2015).
[13] Galiè N, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 37: 67-119 (2016).
[14] Zhuang Y, et al. Randomised study of adding tadalafil to existing ambrisentan in pulmonary arterial hypertension. *Hypertension Research* 37: 507-512 (2014).
[15] Simonneau G, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol.* 62: D34-41 (2013).

Specifically, the wording from the protocol follows:

> *Subjects must not have 3 or more of the following left ventricular disease/dysfunction risk factors:*
>
> - *I. Body Mass Index (BMI) ≥ 30*
> - *II. History of Essential Hypertension*
> - *III. Diabetes Mellitus – any type*
> - *IV. Historical evidence of significant coronary disease established by any one of:*
>   - *history of myocardial infarction*
>   - *history of percutaneous intervention*
>   - *angiographic evidence of CAD (>50% stenosis in at least one vessel), either by*
>   - *invasive angiography or by CT Angiography*
>   - *positive stress test with imaging (either pharmacologic or with exercise treadmill)*
>   - *previous coronary artery surgery*
>   - *chronic stable angina*

The amendment was introduced per ICH E9 Guidance[16] in a manner ensuring that bias was not introduced into the study and thus the integrity of the study was maintained. This is further supported by the concordance between the primary analysis, supportive and sensitivity analyses, all supporting the primary study conclusions. Additionally, all summaries and analyses were produced for both the mITT population (all randomised subjects who received at least one dose of investigational product and met the Protocol Amendment 2 modified inclusion/exclusion criteria, n=500) and the ITT population (all randomised subjects who received at least one dose of investigational product, n=605) and the efficacy and safety results for the (whole) ITT population were consistent with those from the (primary) mITT population.

In summary, the protocol amendment was introduced on the recommendation of the independent scientific steering committee to ensure that subjects with PAH were recruited into the study in a manner that maintained the scientific integrity of the study.

2. How many patients had one or more left ventricular risk factors in the study? What proportion of patients was in each treatment group? What were the primary outcomes for these patients? How do the primary outcomes compare with patients with no LV risk factors?

The number of patients with varying numbers of left ventricular (LV) risk factors is presented in source table 1.4 of the CSR. A summary of the data for the mITT population is presented in the Table 4.

Table 4: Percentage of patients with LV risk factor per randomised treatment arm, mITT population.

Percent Patients with:	Combination (n=253)	Ambrisentan (n=126)	Tadalafil (n=121)
O LV risk factors	35%	38%	40%
1 LV risk factor	40%	35%	34%
2 LV risk factors	26%	27%	26%

[16] ICH harmonised tripartite guideline: Statistical principles for clinical trials E9 (5 February 1998).

The number of patients with 0, 1 or 2 LV risk factors is similar across treatment groups in the mITT population and is similar for patients in the non-mITT population.

GSK has not conducted a specific analysis to compare the primary outcomes for patients with differing numbers of LV risk factors. However these are not anticipated to be different from the primary analysis considering the balance of subjects with risk factors between the treatment groups and the fact that treatment effect was seen in all study populations (ITT, mITT and non-mITT).

3. Please comment on the sensitivity of the Borg Dyspnoea score to detect meaningful differences between groups as used in this study.

The Borg Dyspnoea score is used to score subject symptoms and was not originally designed or validated to detect drug treatment effects. This is the first study where the Borg Dyspnoea score has been used in a study without a placebo control and in an attempt to detect differences between active treatment arms. In prior placebo controlled studies, active treatment has in general confirmed small improvements in the Borg Dyspnoea score, and any significant differences were driven by deterioration in the placebo arm. In this study there was a treatment benefit seen in all treatment arms. As in previous studies the magnitude of effect is small and it would thus appear that the Borg Dyspnoea score is not sensitive enough to detect meaningful treatment differences when comparing active treatment arms.

4. Please confirm that the problems with the search functions of the adverse event database that previously resulted in the inadvertent omission of some adverse events from the PSURs (correspondence dated 24 October 2012) have been resolved?

Following inadvertent omission of some adverse event case reports from Periodic Safety Update Reports (PSURs), Gilead Sciences Inc., GSK's licensing partner and holder of the Global Safety Database for Ambrisentan conducted the following preventive and corrective actions to address the issues, as noted in the report dated October 2012.

- "Gilead has developed and validated an alternative advanced condition that will successfully include cases deemed as "previously not reported" in future PSUR datasets without affecting the cumulative summary tabulation…"
- The omission of cases from PSURs due to the deficient search strategy deployed in Gilead's previous safety database will no longer occur, as the GSK safety database uses a significantly broader and more inclusive search strategy for identifying cases not previously reported that meet the criteria for inclusion in a subsequent PSUR." Corrective actions were all completed by mid 2013 and remain in place.

Safety profile-benefit risk assessment

The safety profile benefit-risk assessment of the ambrisentan/tadalafil combination therapy has been demonstrated as being comparable to the adverse event types reported for ambrisentan alone. The most commonly reported adverse events include headache, fluid retention, gastrointestinal upset (including diarrhoea) and dyspnoea.

In support of the pre ACPM response, GSK have included the PSUR/Periodic Benefit-Risk Evaluation Report (PBRER) for ambrisentan covering the 12 month period from 15 June 2014 to 14 June 2015. During this safety update period, the potential risk of symptomatic hypotension was evaluated, and was reclassified as an important identified risk in the EU-RMP. Consequently, GSK have included this important safety update in the revised Volibris Product Information, as part of the pre ACPM response.

RMP

During the pre-submission phase of the application for the extension of indication for combination therapy of Volibris with tadalafil, GSK applied for a RMP waiver. A RMP waiver was acknowledged by the TGA on the 14 January 2015, where the waiver was

based on the evidence, that the population remained unchanged, with the introduction of combination therapy. Subsequently, the RMP Coordinator had contacted GSK regarding the EU having applied additional risk minimisation activities in the form of Health Care Professional and patient educational materials for the identified risks: "Teratogenicity and Hepatotoxicity," and hence requested an updated EU RMP with an Australian Specific Annex (ASA) to support the current application. As agreed with the RMP Coordinator, GSK will commit to the provision of an updated EU-RMP and ASA prior to the evaluation.

Conclusion

GSK support the opinions of the TGA Delegate in recommending registration of the use of Volibris in combination with tadalafil for the treatment of PAH.

The AMBITION study data supports a complimentary benefit-risk assessment for the registration of Volibris in combination with tadalafil. The safety profile of the combination therapy is similar to Volibris alone, with the exception of hypotension which has been addressed in the revised PI and CMI.

GSK trust that the ACPM will align with the views of the TGA Delegate in recommending registration of the use of Volibris in combination with tadalafil.

Advisory Committee considerations

The Advisory Committee on Prescription Medicines (ACPM) resolved to recommend to the TGA Delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Volibris film coated tablets containing 5 mg and 10 mg of ambrisentan to have an overall positive benefit-risk profile for the amended indication:

> *Volibris in combination with tadalafil is indicated for the treatment of WHO Group 1 pulmonary arterial hypertension in patients with WHO functional class II, III or IV symptoms.*

In making this recommendation, the ACPM was of the opinion that efficacy outcomes can be accepted for all patients with WHO Group I PAH, and that patients with class IV symptoms should not be excluded from the indication.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI.

Specific advice

The ACPM advised the following in response to the specific Delegate's questions on this submission:

- Can the efficacy outcomes be accepted for all patients with WHO Group I PAH given the change of protocol and the resultant exclusion of patients with multiple risk factors for heart failure?

The ACPM was of the opinion that efficacy outcomes can be accepted for all patients with WHO Group I PAH even with the change of protocol and the resultant exclusion of patients with multiple risk factors for heart failure. The ITT population efficacy results for the primary and secondary endpoints were consistent with the mITT population results.

- The study population only enrolled patients with WHO FC class II and III symptoms, although a small number progressed to class IV symptoms. Should patients with class IV symptoms be excluded from the indication?

The ACPM noted that there was minimal evidence on this point. The AMBITION trial only included patients with WHO FC II and III symptoms (approximately 5-7% deteriorated), while Zhuang[17] was an ambrisentan/tadalafil sequential combination trial that included patients with WHO FC II, III and IV symptoms (8.1% FC IV across the treatment arms). The ACPM noted that patients with Class IV symptoms are difficult to study (for example, patients are often immobile), difficult to recruit, and physicians often do not wish to withdraw treatment.

On balance, the ACPM was of the opinion that patients with class IV symptoms should not be excluded from the indication. Clinicians would be advised to follow the ESC/ERS 2015 Guidelines[18] even though there is no direct evidence that combination treatment would help these patients. The ACPM noted that patients with Class III symptoms can rapidly develop Class IV symptoms and therefore should not be excluded as this group would most likely benefit from treatment.

- Has sufficient evidence been provided to support the combination therapy as second line therapy or, based on the evidence should it be for initial therapy only?

The ACPM noted that because both single products have been shown to be effective in their own right in groups of patients, this would suggest that the combination could be used as second line therapy.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

VII. Pharmacovigilance findings II

Risk management plan

The sponsor submitted an EU-RMP (Version 7.4, dated 9 November 2015) with an ASA Version 1.0, dated December 2015, which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 5.

[17] Zhuang Y, et al. Randomised study of adding tadalafil to existing ambrisentan in pulmonary arterial hypertension. *Hypertension Research* 37: 507-512 (2014).
[18] Galiè N, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 37: 67-119 (2016).

Table 5: Ongoing safety concerns.

Important identified risks	Teratogenicity Decreased haemoglobin, haematocrit, anaemia including anaemia requiring transfusion Fluid retention (peripheral oedema, oedema) and heart failure associated with fluid retention Hypersensitivity Worsening dyspnoea of unclear aetiology occurring shortly after starting ambrisentan Drug-drug interaction with cyclosporine A Hepatotoxicity Disease progression or death in patients with idiopathic pulmonary fibrosis Symptomatic hypotension
Important potential risks	Autoimmune hepatitis Testicular tubular atrophy/male infertility
Important missing information	Paediatrics Severe renal impairment Severe hepatic impairment Lactation

The ASA states: "All of the concerns identified in the EU-RMP are relevant for patients in Australia".

RMP reviewer comment

On the basis of the PMAB evaluation of the submitted clinical data, the above summary of safety concerns and missing information appears acceptable. Nevertheless, both the EU-RMP and the ASA make reference to the ongoing ambrisentan long term safety study (GS-US-300-0124), which aims to monitor the long term safety of ambrisentan in subjects with pulmonary hypertension. Consequently, the sponsor should provide compelling justification for why the missing information: 'long term safety' is omitted or otherwise include it as a new safety concern giving due consideration to proposing appropriate pharmacovigilance and risk minimisation activities for this missing information, which only need be reflected in a revised ASA.

In addition, the table 'Major Changes to the Risk Management Plan Over Time' of the EU-RMP appears to be incomplete and only makes reference to Version: 5.0 (dated August 2012). At that time, the EU-RMP states that scarring of the lung without a known cause was added as an identified risk. However, this safety concern is not included in the above summary. Further, this table does not document the reclassification of symptomatic hypotension as an important identified risk instead of as an important potential risk as a safety concern change from Version 7.3 to 7.4. The sponsor should clarify these apparent discrepancies.

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all the specified safety concerns and missing information, including the use of targeted follow-up questionnaires for the important identified risks: 'Teratogenicity', 'Decreased

haemoglobin, haematocrit, anaemia including anaemia requiring transfusion', 'Fluid retention (peripheral oedema, oedema) and heart failure associated with fluid retention', 'Hypersensitivity', 'Hepatotoxicity' and 'Symptomatic hypotension'; and the important potential risk: 'Autoimmune hepatitis'. Copies of these targeted follow-up questionnaires have been provided in an annex of the EU-RMP.

The ASA states: "There are no planned and/or ongoing studies listed in the EU-RMP which is relevant to Australian patients". However, the EU-RMP states for the important identified risk: 'Teratogenicity': "Additional pharmacovigilance which includes: post-marketing surveillance program to collect additional data regarding avoidance of potential foetal teratogenicity risk in USA" and for the missing information: 'Paediatrics': "Additional pharmacovigilance which includes: A paediatric investigative plan (PIP) to evaluate use of ambrisentan in children and adolescents with PAH was approved by the EMA Paediatric Committee (PDCO) and a waiver was granted for children < 1 year of age". Nevertheless, Part III.4: 'Details of outstanding additional pharmacovigilance activities' of the EU-RMP states: "None". No further details of these additional pharmacovigilance activities and no justification for these discrepancies appear to have been provided.

Further, reference is made to the ongoing ambrisentan long term safety study (GS-US-300-0124), which aims to monitor the long-term safety of ambrisentan in subjects with pulmonary hypertension. No protocol for this safety study has been provided and the target date for completion is 4Q 2017.

RMP reviewer comment

As previously mentioned, the sponsor should revise this section of the ASA entirely, as per Section 2: 'Pharmacovigilance Plan' of the ASA template (as found on the TGA website as of 4 May 2015) to clarify the above discrepancies. The sponsor should identify and explain any differences between the additional pharmacovigilance activities proposed in the EU-RMP and those proposed for Australia. Justification for any ambiguity in the EU-RMP should also be included.

Risk minimisation activities

The sponsor concludes that routine risk minimisation activities are sufficient for all the specified safety concerns and missing information.

RMP reviewer comment

In essence the sponsor's justification for not adopting the additional risk minimisation activities for the important identified risks: 'Teratogenicity' and 'Hepatotoxicity' conducted in the EU, is that in Australia routine risk minimisation measures have been effective in the education of prescribers and patients. No evidence has been provided to substantiate these claims and given the emphasis of the use of additional risk minimisation activities in major markets (that is, the US and EU) to mitigate the important identified risks: 'Teratogenicity' and 'Hepatotoxicity' the sponsor's justification is considered inadequate. Consequently, the sponsor should reconsider adopting the additional risk minimisation activities for the important identified risks: 'Teratogenicity' and 'Hepatotoxicity' conducted in the EU. The ASA should be revised accordingly, as per Section 3: 'Risk Minimisation Plan' of the ASA template (as found on the TGA website as of 4 May 2015), including how and when evaluation of additional risk minimisation activities will be undertaken and reported to the TGA. Justification for any ambiguity in the EU-RMP should also be included. Alternatively compelling justification for not adopting similar additional risk minimisation activities for the important identified risks: 'Teratogenicity' and 'Hepatotoxicity' in Australia may be provided.

Reconciliation of issues outlined in the RMP report

The following section seeks to reconcile outstanding RMP issues.

It is considered that the sponsor's response has adequately addressed the outstanding issues identified in the RMP advice.

Updated wording for an RMP condition of registration is therefore recommended.

Background

TGA requested the sponsor revise the ASA to include changes to the format, to identify any differences between pharmacovigilance activities in the EU and Australia, and to identify differences in the risk minimisation activities between the jurisdictions (specifically relating to the safety concerns of teratogenicity and hepatotoxicity).

In response, the revised ASA (Versions 4.0 and 5.0), including healthcare provider and patient educational materials, was submitted to TGA on 9 and 15 March 2016. It is this material which is considered in this advice.

Review

Upon review of the provided ASA and educational material, it is considered that:

- The ASA has been updated, as requested by the TGA, and includes comparison of pharmacovigilance and risk minimisation activities in the EU and Australia. The sponsor has advised that additional risk minimisation activities for the safety concerns of teratogenicity and hepatotoxicity include educational materials in the form of a Healthcare Professional (HCP) information Booklet, a Patient Information Booklet, and a Partner Card.
- The updated ASA includes a table which compares risk minimisation activities between the EU and Australia:
  - Regarding teratogenicity: The sponsor has advised in the ASA that the Partner Card in Australia will not make reference to the product name as per the Medicines Australia Code of Conduct. This is confirmed upon review of the provided Partner Card.
  - Regarding teratogenicity and hepatotoxicity: The sponsor has advised in the ASA that the Patient Information Booklet in Australia will not include a space for HCPs to record ongoing blood test results as per the Medicines Australia Code of Conduct. This is confirmed upon review of the provided Patient Information Booklet.[19]
  - Regarding teratogenicity: The sponsor has advised that the HCP Information booklet in Australia will be updated to reflect local adverse event reporting practices and contain advice reflective of the contraceptive medications and devices currently available in Australia. This is confirmed upon review of the provided HCP Information Booklet.
  - Regarding hepatotoxicity: Advice regarding liver function monitoring is communicated in the provided HCP Information Booklet, and signs, symptoms and the requirement for routine liver function testing is communicated in the Patient Information Booklet.
  - There are no other additional risk minimisation activities advised for the EU or Australia for any other safety concern.

[19] As per the ASA and in accordance with the Medicines Australia Code of Conduct, product branded patient aids should not be removed from the patient's home.

- Regarding effectiveness measure of the education program in Australia, the sponsor advised the following in the ASA (Version 5.0):
  - As an effectiveness measure of the education programme in Australia, GSK Australia will conduct a survey of 5 centres per annum for two years post launch of the combination indication with tadalafil to check the understanding of the materials by HCPs. A Patient Survey will also be conducted through an external third party (market research agency) via telephone interviews. HCPs will identify eligible patients for the survey and seek their consent to participate before sharing their details with the market research agency. A third party to manage the survey is proposed because as a pharmaceutical company, GSK Australia cannot be in direct contact with patients. In recognition of the fact that PAH is a rare disease and that not all newly diagnosed patients would receive treatment with Volibris or wish to participate in the survey, the target sample size will be two patients per centre.
  - GSK will provide the results of the HCP and patient surveys to TGA at 12 and 24 months post launch of the combination therapy indication. An assessment/discussion of the results will be included with a proposal on any further steps which may or may not be required.
  - This plan for effectiveness measure is considered reasonable from a RMP perspective.

- The sponsor was requested to comment on the imagery of the HCP and Patient Information Booklets being promotional in nature. The following response was provided on 15 March 2016:
  - GSK does not agree that the educational materials for Volibris are promotional.
  - GSK has developed materials to provide targeted education for HCPs and patients in order to minimise the risks associated with foetal exposure and the potential risk of hepatotoxicity in patients prescribed Volibris. The materials have been developed to be engaging documents and are fully aligned with critical information from the Australian PI and CMI.
  - In accordance with the Medicines Australia Code of Conduct, "promotion" refers to "any statement which conveys the positive attributes of a product which extend beyond a simple non-qualitative or quantitative description of the therapeutic category or approved indication for the purpose of encouraging the usage of that product". Based on this definition, GSK believes that both the HCP and patient booklets are non-promotional in nature.
  - The patient booklet is based entirely on information contained within the TGA approved CMI. The purpose of the booklet is to educate the patient and promote the quality use of our product by providing information on the mode of action, dosage, precautions and any special instructions for use. Importantly, the booklet will only be provided to and seen by patients once a decision to prescribe the product has been made. Every effort has been made to ensure this with the inclusion of the following wording on the front cover: "INFORMATION FOR PATIENTS WHO HAVE BEEN PRESCRIBED VOLIBRIS. FOR SPECIALISTS ROOM ONLY. NOT TO BE KEPT IN PATIENT WAITING AREAS".
  - The imagery that appears is in line with the global imagery used for the brand. This imagery is in no way intended to imply a benefit regarding treatment with Volibris. The use of a comforting gesture on the front page of this piece is aimed exclusively at supporting and reassuring a patient during their diagnosis and treatment of a severe and life threatening condition.

- Similarly, the booklet for healthcare professionals contains no promotional claims within the document. All of the information provided is based on that contained within both the TGA approved PI and CMI and is dedicated purely to ensuring the quality use of our product.
- Finally, GSK notes that use of graphics in educational materials for Australia is not unique to Volibris and the TGA have approved such materials associated with RMPs in the past. Indeed, a recent example is the educational materials for a vaccine, which were submitted to TGA as part of ASA Version 5. TGA did not raise any comments on the graphics included in the educational materials and the RMP was found to be acceptable.
- The following is noted regarding promotional elements in the EU Guideline on Good Pharmacovigilance Practices (GVP) – Module XVI (Rev 1; EMA/204715/2012[Rev 1]):
  - Promotional elements, either direct or veiled (for example, logos, product brand colours, suggestive images and pictures), should not be included and the focus of the educational material should be on the risk(s) related to the product and the management of those risk(s) requiring additional risk minimisation.
- Upon consideration of the sponsor's response and the GVP guidance, the educational materials are considered appropriate from a RMP perspective.

- It is considered that the sponsor's response has satisfied the outstanding RMP recommendations made in the RMP advice. Specifically:
  - To update the ASA to better reflect pharmacovigilance and risk minimisation activities for Australia: This has been satisfied as above.
  - Address issues related to the Australian HCP and Patient educational materials as attachments to the ASA: This has been satisfied as above.

VIII. Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Volibris containing ambrisentan for the **new** indication:

> *Volibris in combination with tadalafil is indicated for the treatment of WHO Group 1 pulmonary arterial hypertension in patients with WHO functional class II, III or IV symptoms.*

The **full** indications are now:

> *Volibris is indicated for the treatment of:*
>
> - *idiopathic pulmonary arterial hypertension (PAH),*
> - *pulmonary arterial hypertension 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 pulmonary arterial hypertension in patients with WHO functional class II, III or IV symptoms.*

Specific conditions of registration applying to these goods

- The Volibris RMP, as qualified by the ASA, and any subsequent revisions, as agreed with TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Volibris at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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