Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for macitentan

Proprietary Product Name: Opsumit

Sponsor: Actelion Pharmaceuticals Australia Pty Ltd

April 2014

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 <http://www.tga.gov.au>.

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- An Australian Public Assessment Record (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, in that it will provide 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.

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List of commonly used abbreviations

Abbreviation	Meaning
ACT-064992	Macitentan
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC_{0-t}	Area under plasma concentration-time curve from zero to time t of the last measured concentration above the limit of quantification
$AUC_{0-\infty}$	Area under plasma concentration-time curve from zero to infinity
bd	Twice daily
BP	Blood pressure
bpm	Beats per minute
CI	Confidence interval
CL	Confidence limit
CRF	Clinical report form
CSR	Clinical Study Report
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
EOS	End-of-study
EOT	End-of-treatment
EU	European Union
FC	(WHO) Functional Class
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	Heart rate
IPF	Idiopathic pulmonary fibrosis
L	Litre

Abbreviation	Meaning
m	metre
MAD	Multiple-ascending-dose
mg	Milligram
mL	Millilitre
ms	Millisecond
NOAEL	No observed adverse effects level
PAH	Pulmonary arterial hypertension
PD	Pharmacodynamics
PK	Pharmacokinetics
PR	Pulse rate
qd	Once daily
SAD	Single-ascending-dose
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
$t_{½}$	Half-life associated with the terminal slope
TGA	Therapeutic Goods Administration
ULN	Upper limit normal
US	United States

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	31 January 2014
Active ingredient:	Macitentan
Product name:	Opsumit
Sponsor's name and address:	Actelion Pharmaceuticals Australia Pty Ltd Suite 6/13B Narabang Way BELROSE NSW 2085
Dose form:	Film coated tablet
Strength:	10 mg
Containers:	Blister pack and bottle
Pack sizes:	Blister pack – 3, 6, 9 and 30 tablets Bottle – 30 tablets
Approved therapeutic use:	*Opsumit; as monotherapy or in combination with approved PAH treatments (phosphodiesterase-5 inhibitors or inhaled prostanoids), is indicated for the treatment of:* · *idiopathic pulmonary arterial hypertension* · *heritable pulmonary arterial hypertension* · *pulmonary arterial hypertension associated with connective tissue disease* · *pulmonary arterial hypertension associated with congenital heart disease with repaired shunts* *in patients with WHO Functional Class II III or IV symptoms.*
Route of administration:	Oral
Dosage:	10 mg daily in patients 12 years old and above.
ARTG numbers:	205624: Blister pack 205427: Bottle

Product background

Opsumit (macitentan) is a new chemical entity for the treatment of pulmonary arterial hypertension (PAH) following its designation as an orphan drug in July 2012 'For the treatment of PAH' Macitentan belongs to the same class of pharmaceuticals as bosentan and ambrisentan and the former sitaxentan (withdrawn globally due to liver toxicity) which are orally active endothelin receptor antagonists (ERAs). Macitentan, like bosentan, is a dual endothelin A and B receptor antagonist which is different to ambrisentan and is specific for endothelin type A receptors.

The pathological changes that occur in PAH are thought to be mediated through an up-regulated endothelin-1 (ET-1) system, defective prostacyclin synthase activity and abnormalities of the nitric oxide pathway. Current treatments for PAH are aimed at these three pathways: ERAs (inhibit the effects of elevated ET-1 and thus reduce vasoconstriction, smooth muscle cell proliferation and pulmonary vessel fibrosis), prostacyclin analogs (relax and reduce proliferation of vascular smooth muscle cells) and phosphodiesterase type 5 (PDE-5) inhibitors (potentiate the anti-platelet, antiproliferative and vasodilatory effects of nitric oxide).

Specific pharmaceutical treatments registered for the treatment of PAH include oral bosentan, ambrisentan, tadalafil and sildenafil, inhaled nitric oxide and iloprost, intravenous (IV) epoprostenol and subcutaneous (SC) treprostinil. Recent orphan designations for PAH include imatinib and riociguat. The sponsor claims that macitentan potentially has better efficacy and safety characteristics compared to current ERAs with high affinity and sustained occupancy of endothelin receptors, pharmacokinetic (PK) characteristics that are consistent with once daily dosing and, unlike current therapies which have mainly shown a benefit in terms of symptom relief via improvements in exercise capacity, has demonstrated benefit for long term clinical outcome in terms of morbidity and mortality.

Opsumit has not been previously considered by ACPM.

This AusPAR describes the application by Actelion Pharmaceuticals Ltd (the sponsor) to register Opsumit (macitentan), a new chemical entity, for use in the long-term treatment of PAH.

Regulatory status

The product received initial ARTG Registration on 5 February 2014.

The international regulatory status of macitentan is included in Table 1.

Table 1: International regulatory status

Country	Submission Date	Marketing Application Status
United States	19 October 2012	Approved 18 October 2013
European Union	24 October 2012	Positive CHMP Opinion 25 October 2013
Switzerland	10 December 2012	14 Feb 2014
Canada	21 December 2012	6 November 2013

Country	Submission Date	Marketing Application Status
New Zealand	17 February 2014	Review ongoing

Product Information

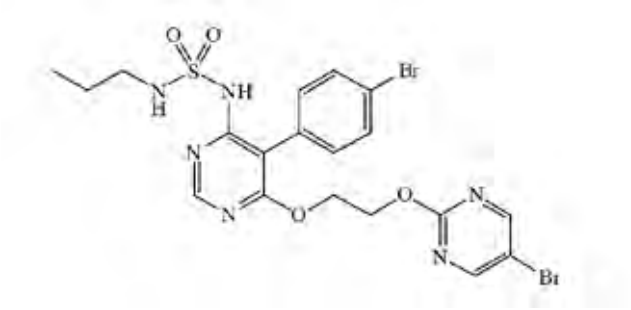
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Macitentan is made by chemical synthesis. It is an achiral molecule. Various polymorphic forms were shown to exist but the most thermodynamically stable form was used in the manufacture of the finished product. Macitentan was shown to be non-hygroscopic. The pKa of macitentan is 6.2.

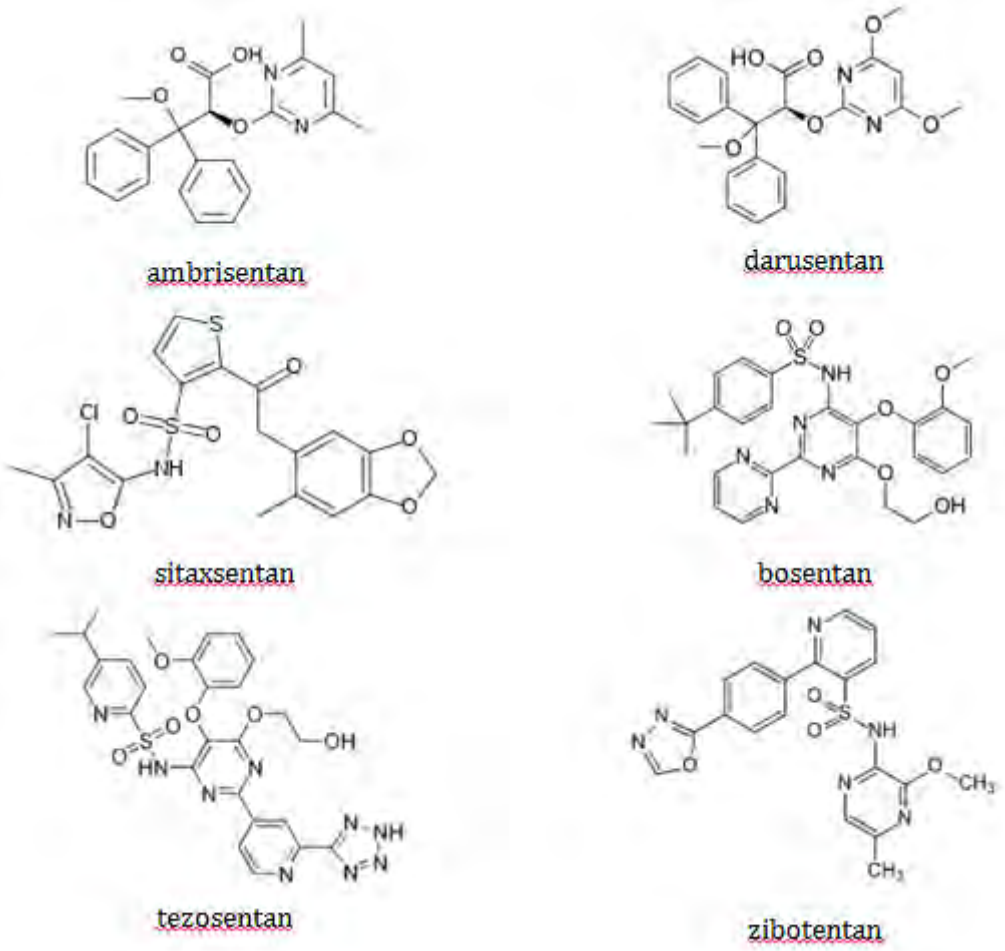
Figure 1: Structure of macitentan



Macitentan

The API is structurally related to other non-peptide PAH ERA treatments such as bosentan, ambrisentan, darusentan, tezosentan, zibotentan and sitaxsentan. The structures for these are below.

Figure 2: Structures of other non-peptide PAH endothelin receptor antagonist treatments



Macitentan is insoluble in aqueous solutions. The solubility of macitentan in organic solvents is shown in the table below:

Table 2: The solubility of macitentan in organic solvents

Solvent	Solubility	Solubility in mg/mL
Acetonitrile	soluble	approx. 40
Ethyl acetate	soluble	approx. 50
Acetone	soluble	approx. 100
Tetrahydrofurane	freely soluble	> 600
Methylene chloride	very soluble	> 1000
Dimethylsulfoxide	freely soluble	> 400
N,N-dimethylformamide	freely soluble	> 500
Methanol	slightly soluble	approx. 5
Ethanol	slightly soluble	approx. 2
Isopropanol	very slightly soluble	< 1
1-octanol	very slightly soluble	< 1
Toluene	slightly soluble	approx. 6
Polyethylene glycol	slightly soluble	approx. 4
Diethyl ether	slightly soluble	approx. 5
Propylene glycol	not soluble	-
Hexane	not soluble	-

Appropriate particle size controls have been applied by the finished product manufacturer. Impurity controls are acceptable.

Tablets

The proposed OPSUMIT tablets are film-coated, immediate release tablets. They are not scored.

The formulation is conventional. They are presented in 3, 6, 9, 30 tablets PVC/PE/PVDC/Al blister pack and in 30 tablets HDPE bottle (with a Child Resistant Closure (CRC)).

A capsule formulation was initially developed to provide dose flexibility. The capsule formulation was used in early Phase 1 and Phase 2 studies. To overcome chemical stability issues observed, a tablet formulation was developed and scaled-up. The film-coated tablet formulation was used in clinical Phases I, II and III. The tablet formulation used in these studies is the same as that proposed for registration. The PK profile for the capsule formulation was compared to the tablet formulation (Study AC-055-108).

The proposed shelf life is 24 months, store below 30°C and protected from moisture in PVC/PE/PVdC blister packs and HDPE bottles. No changes on storage were detected.

Chemistry and quality control aspects are considered acceptable.

Biopharmaceutics

The PK is dose-proportional up to and including 30 mg, after repeated administration. Maximum plasma concentrations of macitentan are achieved about eight hours after administration. Thereafter, plasma concentrations of macitentan and its active metabolite decrease slowly, with an apparent elimination half-life of approximately 16 hours and 48 hours, respectively.

The justification for not conducting an absolute bioavailability was provided which states that the poor aqueous solubility and stability presented barriers to designing an IV and oral solution formulations. The absolute bioavailability was simulated using a physiologically based PK computer model with generic, physiological, and demographic variables using Monte Carlo methods and equations derived from population database obtained from literature sources. The results indicated an oral bioavailability of 74% (geometric mean, 95% CI: 72%, 77%).

An exploratory, open-label, randomised, two-period, two-treatment, crossover study (Study AC-055-103) was conducted to investigate the effect of food on the PK of ACT-064992 and ACT-132577 in healthy male subjects. The 90% CI's of the geometric mean ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were between 80-125%. It can be concluded that PK of both ACT-064992 and its metabolite, ACT-132577, were unaltered in the presence of food.

A single-centre, open-label, randomised, two-way crossover study (Study AC-055-108) was conducted to investigate the relative bioavailability of a single-dose tablet and capsule formulation of ACT-064992 in healthy male subjects. The relative bioavailability study serves as a bridging study between the pivotal and early clinical trial formulations. It is noted that mean C_{max} for ACT-064992 was approximately 20% lower after ingestion of the tablet compared to the capsule formulation. Consequently, the lower end of the 90% CI of the geometric mean ratio of C_{max} failed to comply with the accepted bioequivalence range of 80%-125%. The 90% of the geometric mean ratio of AUC_{0-t} was within 80-125% and spanned unity (0.89-1.01). The intended use of the drug is as a chronic, multiple dose regime and hence the same steady-state plasma exposures are expected to be achieved of both the active and the metabolite during ongoing therapy.

Quality summary and conclusions

Registration is recommended with respect to chemistry, quality control and bioavailability aspects.

III. Nonclinical findings

Introduction

The Sponsor has submitted a comprehensive dossier of high quality studies in support of the efficacy and safety of the novel, sulfamide-type, ERA, macitentan. The pivotal toxicological studies were performed to Good Laboratory Practice (GLP) standards by prominent, independent laboratories.

Pharmacology

Primary pharmacology

PAH is associated with marked increases in the plasma concentration of the peptide ET-1 and with thickening of the artery wall, and can be explained as deriving (at least in part) from the vasoconstrictive and mitogenic actions of ET-1. Macitentan has been developed as an antagonist to the binding of ET-1 to both the ET_A and ET_B receptors. In this regard, macitentan is similar to another ET-1 receptor antagonist, bosentan, but differs from ambrisentan, which is a selective inhibitor of the ET_A receptor. There has been considerable debate about the merits of treating PAH patients with antagonists that inhibit one versus both ET-1 receptors (particularly given that activation of the ET_B receptor can be vasodilatory). Nevertheless, there is evidence that both ET-1 receptors can contribute to vasoconstriction, and this was a basis for the development of macitentan.

Both macitentan and its major plasma metabolite, ACT-132577, acted as competitive antagonists of ET_A and ET_B receptors in in vitro biochemical assays and in functional assays using isolated rat tissues. Macitentan was a more potent antagonist than ACT-132577: IC_{50} values for inhibition of ET-1 binding to the human ET_A receptor were 0.5 and 3.4 nM and to the human ET_B receptor were 391 and 987 nM for macitentan and ACT-132577, respectively. In contrast, another major human plasma metabolite, ACT-373898, showed no antagonistic activity towards ET-1 receptors.

In vitro comparison of the inhibition of ET-1-induced intracellular Ca^{2+} release in human pulmonary arterial smooth muscle cells suggested that macitentan is a more potent antagonist than bosentan and has similar potency to ambrisentan. Similarly, under in vivo conditions, macitentan showed ten-fold higher potency for binding to ET-1 receptors in rats than bosentan. Following drug wash-out from treated smooth muscle cells, return of ET-1 responsiveness was much slower after macitentan treatment. Estimated receptor occupancy half-life values were 40 second (ambrisentan), 70 seconds (bosentan), and 17 minutes (macitentan). This result indicates that macitentan is an orthosteric competitive antagonist with a long receptor occupancy half-life.

The ability of macitentan to lower blood pressure (BP) or inhibit induction of pulmonary fibrosis was tested in rat salt-induced hypertension models and in rat bleomycin- or monocrotaline-induced PAH models. In each of these models, macitentan was approximately ten-fold more potent than bosentan. Macitentan was also shown to produce a significant additional lowering of BP when administered to hypertensive rats following a maximally effective dose of ambrisentan. Conversely, dosing with ambrisentan following a maximally effective dose of macitentan or ambrisentan did not produce additional BP lowering.

Secondary pharmacodynamics and safety pharmacology

None of 63 different receptors and enzymes showed more than 50% inhibition of radioligand binding in the presence of 10 μM macitentan, indicating that it is highly selective for the ET_A and ET_B receptors.

Further in vitro studies showed that macitentan and its metabolite ACT-132577 inhibited human sodium-dependent taurocholate co-transporting polypeptide (transports bile salts from blood into hepatocytes) with IC_{50} values of 19 μM and 14 μM, respectively, and inhibited the bile salt export pump with IC_{50} values of 18 μM and 50 μM, respectively. Steady-state total plasma concentrations of macitentan and ACT-132577, in healthy male subjects receiving the recommended clinical dose of 10 mg once daily, were about 0.63 μM and 1.5 μM, respectively (clinical report no. D-06.044). At those concentrations, binding of macitentan and ACT-132577 to human plasma proteins in vitro was about 99.6 % and 99.5 %, respectively, suggesting free plasma concentrations of approximately 2.5 nM and 7.3 nM. As cellular uptake of macitentan and ACT-132577 is largely driven by passive diffusion, it is likely that the free steady-state concentrations of both compounds are similar in hepatocytes and in plasma. Accordingly, it appears unlikely that clinical levels of macitentan and ACT-132577 would significantly influence bile salt transport.

Human hepatotoxicity induced by bosentan has been related to its ability to increase plasma bile salt levels in humans (Fattinger et al. 2001[1]), due, at least in part, to inhibition of the human bile salt export pump (Mano et al. 2007[2]). Bosentan may be a less potent inhibitor of the human bile salt export pump than macitentan (Mano et al. 2007), although other factors, such as active accumulation of bosentan in hepatocytes, might explain the apparent discrepancy that bosentan increased plasma bile salt levels in rats (Fattinger et al. 2001) but macitentan showed no consistent effects on plasma bile salt levels in rats and other animals. Indeed, rats dosed with macitentan at 10 or 250 mg/kg/day for 26 weeks showed statistically significant decreases in plasma bile salt levels.

Safety pharmacology studies examined macitentan effects on the central nervous system (CNS), cardiovascular, and respiratory systems. At doses up to 100 mg/kg (expected to produce a C_{max} approximately 50-times that in humans receiving the maximum recommended dose), macitentan had no effect on respiratory parameters or on behavioural and physiological variables related to the central and peripheral nervous systems of the rat. Macitentan had a negligible effect on the hERG K+ current in CHO cells (18% reduction of current amplitude at 10 μM; approximately 2000-fold higher than the anticipated unbound plasma concentrations of macitentan and ACT-132577 in patients receiving the recommended dose). ACT-132577 showed similar effects.

Guinea-pigs given IV macitentan at 10 mg/kg showed no effects on heart rate or electrocardiogram intervals. Beagle dogs, orally dosed with macitentan, showed a dose-dependent decrease in mean, systolic, and diastolic arterial BP (statistically significant at ≥ 0.3 mg/kg), which at 5 and 30 mg/kg was associated with a slight, compensatory increase in heart rate (no effect on electrocardiogram parameters). C_{max} values for macitentan in dogs dosed at 0.3 mg/kg were similar to human values, whilst dogs dosed at 5 mg/kg had values about 10-times those of humans receiving 10 mg/day.

[1] Fattinger K., Funk C., Pantze M., et al. 2001. The endothelin antagonist bosentan inhibits the canalicular bile salt export pump: a potential mechanism for hepatic adverse reactions. Clinical Pharmacology and Therapeutics, 69: 223–231

[2] Mano Y., Usui T. and Kamimura H. 2007. Effects of bosentan, an endothelin receptor antagonist, on bile salt export pump and multidrug resistance-associated protein 2. Biopharmaceutics and Drug Disposition, 28: 13–18

Pharmacokinetics

Absorption: Following oral dosing, macitentan generally showed fairly slow absorption with t_{max} occurring at approximately one to two hours (mice),approximately two to six hours (rats and dogs), and approximately eight hours (humans). Bioavailability showed marked dose dependence in rats, increasing from 30 to 90% over the range 1 to 30 mg/kg, but was approximately 80% at all doses over the range 0.3–10 mg/kg in dogs. Exposure to macitentan in humans showed an approximately linear increase with dose over the range 1–10 mg/day but a somewhat less than proportional increase at 30 mg/day. At the higher doses used in animal studies, exposure generally increased considerably less than proportionally with dose.

Distribution: As indicated above, plasma protein binding of macitentan and its major metabolite, ACT-132577, was high in all species examined (> 98% over the range 0.1 to 300 µg/mL). Albumin is probably the major plasma protein responsible for macitentan binding, with a lesser contribution from α1-acid glycoprotein. Volume of distribution at steady state, for rats and dogs, was greater than total body water indicating distribution of macitentan into tissues. Radiolabelled macitentan showed a wide tissue distribution in rats after oral administration. At eight hours after dosing (time of peak concentration for plasma and most tissues), the highest levels of radioactivity were in liver, kidney cortex, blood, lung, and myocardium. Significant radioactivity was found in both bile ducts and urinary bladder, suggesting elimination by both routes. Tissues showing notably low radioactivity concentrations at all time-points included CNS (brain and spinal cord), testis, and lens (body and wall). There may be a minor degree of binding of macitentan to melanin. Comparison of the radioactivity distribution in control and bleomycin-treated (induces pulmonary fibrosis) rats suggested that radioactivity was preferentially located at diseased sites.

Metabolism: The major route of macitentan metabolism in all species examined (rat, dog, and human, plus more limited results for mouse, pig, and monkey) involved removal of the propylaminosulfone side chain. This removal could take place in one step, to generate ACT-080803 (the major metabolite in faeces, and also present in urine), or in two steps via the depropylated intermediate ACT-132577. In all species examined, ACT-132577 was the major metabolite present in plasma. ACT-132577 is an antagonist of ET-1 receptors (see above) and also has a considerably longer plasma half-life than the parent compound (t½ values for male rats were approximately two and eight hours, and for humans were approximately 15 and approximately 50 hours, for macitentan and ACT-132577, respectively). Another route of macitentan metabolism is removal of the bromopyrimidine moiety to produce ACT-373898, which was identified as a major metabolite in human plasma but was only found at very low concentrations (generally less than a thousandth of that for macitentan or ACT-132577) in plasma from mice, rats, and dogs. Glucose and glucuronic acid conjugates of macitentan metabolites were also identified in bile and urine from rats and dogs. These conjugates in bile were cleaved by the gut flora and subsequently hydrolysed to ACT-080803.

CYP3A4 was identified as the major enzyme responsible for the production of ACT-132577 in man, with CYP2C19 perhaps playing a minor role. Studies in mice, rats, and dogs showed that macitentan and ACT-132577 had the ability to increase the expression of mRNAs encoding macitentan-metabolising enzymes and to increase the activity of these enzymes. However, the animal studies used drug exposures exceeding the clinical range and it was questionable whether similar effects would be seen in patients. Indeed, repeat-dose studies in animals generally showed an initial decline in exposure levels and no evidence for significant accumulation of macitentan or ACT-132577, whereas the opposite appeared true of human studies.

Excretion: Bile was the major route of excretion in both rats and dogs. Following administration of radiolabelled macitentan to male Wistar rats, recovery from bile

represented approximately 50 to 70% of the dose, whilst faeces and urine accounted for approximately 10 to 25% and approximately 20% of the dose, respectively. In humans, urine was the major route of excretion (accounting for approximately70% of the recovered dose), with the remainder in faeces.

Conclusion: As noted above, while there were some differences in the metabolism and PK of macitentan between humans and the tested animal species these were not sufficient to preclude the validity of the animal models for the assessment of macitentan toxicity.

Pharmacokinetic drug interactions

The ability of macitentan, ACT-132577, and ACT-080803 to inhibit human CYPs was tested using liver microsome preparations and recombinant enzymes. Micromolar concentrations of these compounds were required to inhibit CYP activities. As patient free plasma concentrations of these compounds are estimated to be in the nanomolar range (see above), it is unlikely that they will have a significant effect on CYP activities.

Cellular uptake of macitentan appeared to be by passive diffusion and was not affected by P-gp inhibition. Conversely, macitentan, at concentrations up to 100 μM, had no effect on the transport of P-gp substrates. In similar studies, inhibition of various human organic anion transporting polypeptides (OATP1B1, OATP1B3, and OATP2B1) had no effect on the uptake of macitentan and ACT-132577. Both compounds were generally moderate to weak OATP inhibitors, although macitentan showed significant inhibitory activity towards OATP2B1 (IC^{50} = 0.8 μM). OATP2B1 mediates uptake from blood into hepatocytes of various substrates, including the bile salt taurocholate (The International Transporter Consortium 2010). As detailed above, patient free plasma concentrations are markedly lower than 0.8 μM. Hence, macitentan and ACT-132577 are unlikely to change the PK of co-administered drugs via inhibition of OATP transporters.

Toxicology

Acute toxicity

Single-dose toxicity studies were performed with mice and rats. For both species, the maximum, non-lethal, orally administered dose of macitentan was ≥ 2000 mg/kg.

Repeat-dose toxicity

Pivotal studies were performed in mice, rats, and dogs at durations of up to 13, 26, and 39 weeks, respectively. All studies used once daily, oral dosing, which is consistent with the mode and frequency of clinical dosing. The design of the studies was consistent with the relevant EMA guideline (CPMP/SWP/1042/99 Rev 1).

Relative exposure

The approach of using combined AUC values for macitentan and ACT-132577 for exposure comparison was not considered valid as the pharmacological activity of ACT-132577 is significantly less than the parent. Relative exposures to macitentan and ACT-132577 attained at the NOAEL (no observed adverse effects level) doses were low to modest: 12 to 18 for B6C3F1 mice dosed for 13 weeks; approximately two to 12 for Wistar rats dosed for 13 or 26 weeks; and about one to 11 for beagle dogs dosed for 13 or 39 weeks (see Table 3).

Table 3: Relative exposure in repeat-dose toxicity and carcinogenicity studies

Species	Study duration (number)	Dose (mg/kg/day)[b]		AUC_{0-24h} (µg·h/mL)		Exposure ratio[c]	
				Macitentan	ACT-132577	Macitentan	ACT-132577
Mouse (CD-1)	13 weeks (T-05.155)	75, 300, 900	♂	428, 528, 571 (day 92)	706, 1113, 1676 (day 92)	79, 98, 106	45, 72, 108
			♀	670, 823, 953 (day 92)	928, 1409, 2608 (day 92)	124, 152, 176	60, 91, 168
	13 weeks (T-07.208)	5, 20, 75	♂	19.7, 75.5, 224 (day 88)	72.3, 219, 535 (day 88)	3.6, 14, 41	4.7, 14, 34
			♀	35.8, 127, 358 (day 88)	89.6, 255, 641 (day 88)	6.6, 24, 66	5.8, 16, 41
Mouse (B6C3F1)	13 weeks (T-08.388)	10[d], 50, 400, 1500	♂	>66, 307, 653, 1090 (day 88)	185, 632, 1600, 2710 (day 88)	>12, 57, 121, 202	12, 41, 103, 174
			♀	99.7, 428, 1140, 1340 (day 88)	238, 768, 1720, 2970 (day 88)	18, 79, 211, 248	15, 49, 111, 191
	2 years (T-09.160) [carcinogenicity]	5, 30, 100, 400	♂	31.1, 261, 405, 751 (week 26)	106, 574, 907, 1750 (week 26)	5.8, 48, 75, 139	6.8, 37, 58, 113
			♀	60.7, 392, 751, 1110 (week 26)	129, 609, 1190, 1920 (week 26)	11, 73, 139, 206	8.3, 39, 77, 124

Species	Study duration (number)	Dose (mg/kg/ day)[b]		AUC_{0-24h} (µg·h/mL)		Exposure ratio[c]	
				Macitentan	ACT-132577	Macitentan	ACT-132577
Species	Study duration (number)	Dose (mg/kg/ day)[b]		AUC_{0-24h} (µg·h/mL)		Exposure ratio[c]	
				Macitentan	ACT-132577	Macitentan	ACT-132577
Rat (SD)	4 weeks (T-04.043)	50, 150, 450, 1500	♂	114, 200, 327, 365 (day 28)	288, 499, 695, 925 (day 28)	21, 37, 61, 68	19, 32, 45, 60
			♀	490, 776, 1276, 1588 (day 28)	342, 556, 497, 1684 (day 28)	91, 144, 236, 294	22, 36, 32, 108
Rat (Wistar)	13 weeks (T-04.076)	10, 50, 250	♂	11.3, 34.1, 74.2 (week 13)	44.9, 142, 324 (week 13)	2.1, 6.3, 14	2.9, 9.1, 21
			♀	66.9, 170, 446 (week 13)	52.4, 169, 490 (week 13)	12, 31, 83	3.4, 11, 32
	26 weeks (T-05.045)	10, 50, 250	♂	9.11, 30.2, 39.5 (week 26)	41.0, 122, 210 (week 26)	1.7, 5.6, 7.3	2.6, 7.9, 14
			♀	67.4, 229, 371 (week 26)	62.1, 214, 467 (week 26)	12, 42, 69	4.0, 14, 30
	2 years (T-09.159) [carcinogeni	♂ = 10, 50, 250 ♀ = 10, 50/25,	♂	18.3, 45.1, 97.4 (week 26)	72.7, 164, 291 (week	3.4, 8.4, 18	4.7, 11, 19

Species	Study duration (number)	Dose (mg/kg/day)[b]		AUC_{0-24h} (µg·h/mL)		Exposure ratio[c]	
				Macitentan	ACT-132577	Macitentan	ACT-132577
	city]	250/50			26)		
			♀	104, 227, 506 (week 26)	98.2, 227, 497 (week 26)	19, 42, 94	6.3, 15, 32
Dog (beagle)	2 weeks (T-04.048)	30, 100, 300, 600	♂	37, 106, 87, 192 (day 14)	–	6.9, 20, 16, 36	–
			♀	37, 56, 95, 153 (day 14)	–	6.9, 10, 18, 28	–
	4 weeks (T-04.049)	5, 50, 500/250	♂	14.7, 39.1, 44.9 (day 27)	146, 1362, 2525 (day 27)	2.7, 7.2, 8.3	9.4, 88, 162
			♀	10.5, 46.5, 84.4 (day 27)	164, 1223, 3129 (day 27)	1.9, 8.6, 16	11, 79, 201
	13 weeks (T-04.077)	2, 5, 30, 100	♂	9.16, 15.4, 55.1, 60.2 (week 13)	56.7, 178, 966, 1990 (week 13)	1.7, 2.9, 10, 11	3.6, 11, 62, 128
			♀	7.33, 24.4, 34.3, 101 (week 13)	66.4, 160, 843, 1580 (week 13)	1.4, 4.5, 6.4, 19	4.3, 10, 54, 102
	39 weeks (T-05.027)	5, 30, 100/75	♂	9.88, 22.9, 31.3 (week 39)	114, 465, 942 (week 39)	1.8, 4.2, 5.8	7.3, 30, 61

Species	Study duration (number)	Dose (mg/kg/day)[b]		AUC_{0-24h} (µg·h/mL)		Exposure ratio[c]	
				Macitentan	ACT-132577	Macitentan	ACT-132577
			♀	<u>6.14</u>, 21.9, 37.9 (week 39)	<u>77.8</u>, 341, 1200 (week 39)	<u>1.1</u>, 4.1, 7.0	<u>5.0</u>, 22, 77
Human (healthy volunteers)	steady state – 10 days (D-06.044) (AC-055-102)	[10 mg]	♂	5.40	15.54	–	–

[a]All listed studies are GLP compliant; [b]doses given po (gavage); [c]animal:human plasma AUC_{0-24h}; [d]values at NOAEL are bolded and underlined (where no value so indicated NOAEL = < LD).

Major toxicities

Major test article-related findings occurred in liver, haemopoietic system, testis, and vasculature. Exposure ratios mentioned below refer to macitentan rather than total active moiety as ACT-132577 has significantly less activity than the parent compound.

Mouse 13-week dosing studies demonstrated centrilobular hepatocytic hypertrophy and bile duct reactive hyperplasia, disturbances in liver homeostasis (decreases in cholesterol, triglycerides, and albumin), and liver toxicity (hepatocytic necrosis [often associated with inflammation] and increases in plasma AST and ALT levels). However, these effects were generally only prominent in groups given relatively high doses of macitentan (exposure ratios of ≥ 14 and > 50 for CD-1 and B6C3F1 mice, respectively). Rats dosed for 13 or 26 weeks with macitentan showed centrilobular hepatocytic hypertrophy (reversible after drug-free recovery period), but no evidence of liver toxicity, except for animals that died prematurely after dosing at 1500 mg/kg (exposure ratio of > 60). Similarly, dogs dosed for up to 39 weeks (exposure ratio of approximately 6 for macitentan) showed centrilobular hepatocytic hypertrophy (reversible after drug-free recovery period), but no evidence of liver toxicity. These results suggest that macitentan does not pose a pronounced risk for liver toxicity in patients. This is significant because other sulfonamide-type ET-1 receptor antagonists, bosentan and sitaxentan, have been linked to cases of acute liver injury (Hoeper 2009[3]).

Many of the studies indicated effects of the test article on the haemopoietic system; however, the effects were inconsistent or not apparent between species. CD-1 mice dosed for 13 weeks at ≥ 75 mg/kg/day (exposure ratio > 50) showed increases in red blood cell (RBC) count and extramedullary haemopoiesis in the spleen, and increases in bone marrow myelopoiesis. Male (but not female) Wistar rats dosed for 13 or 26 weeks at 250 mg/kg/day (exposure ratio 7 to 14) showed moderate, reversible increases in platelet counts and activated partial thromboplastin time. Dogs dosed for 39 weeks at 100/75 mg/kg/day (exposure ratio about six) also showed moderate increases in platelet counts,

[3] Hoeper M.M. 2009. Liver toxicity: the Achilles' heel of endothelin receptor antagonist therapy? European Respiratory Journal, 34: 529–530

as well as decreased RBC counts. Premature decedents from the dog study (mostly dosed at 100/75 mg/kg/day) showed anaemia and low neutrophil counts. Given the fairly high exposure ratios for the haemopoietic changes they are considered unlikely to be of clinical relevance.

Testicular effects were seen in both rat and dog studies: tubular dilation and tubular atrophy (exposure ratio ≥ 14 for 13 weeks dosing at 250 mg/kg/day) and an increased incidence of morphologically abnormal sperm (exposure ratio > 5 for 26-weeks dosing at 50 mg/kg/day) in rats, and tubular dilation (exposure ratio > 4 for 39-weeks dosing at 30 mg/kg/day) and hypospermatogenesis (exposure ratio > 6 for 39-weeks dosing at 30 mg/kg/day) in dogs. These effects are thought to derive, at least in part, from inhibition of ET-1-induced contraction of peritubular myoid cells; a process that normally impels spermatozoa towards the rete testis (Tripiciano et al. 1996[4]). The testicular effects in animals were reversed after a drug-free period, but are of potential relevance to human use given the relatively low exposure margins.

Premature decedents from the 39-week dog study (mostly dosed at 100/75 mg/kg/day) showed multicentric arteritis/periarteritis (a range of vascular lesions extending from a focal mononuclear cell infiltration, to extensive mixed inflammatory lesions involving medial fibrinoid necrosis) in the heart and also affecting other organs including lung, thymus, kidney and vessels around the optic nerve. Arteritis/periarteritis was also seen in survivors dosed at ≥ 5 mg/kg/day (exposure ratio > 1), and extramural arterial intimal thickening was seen in survivors dosed at ≥ 30 mg/kg/day (exposure ratio > 4). Various other ET-1 receptor antagonists, as well as a diverse group of vasodilators, have been shown to induce arteritis in dogs (for example, Jones et al. 2003[5], McDuffie et al. 2006[6]).

Rat studies indicated increases in thyroid weight and thyroid follicular cell hypertrophy (particularly in males) following repeat dosing with macitentan. This is considered a species-specific, adaptive response, related to increased thyroxine clearance following microsomal enzyme induction, (particularly induction of thyroxine glucuronidation) and to the short half-life of thyroxine in rats (for example, Vansell and Klaassen 2001[7]). Male rats dosed with macitentan for 26 weeks at 250 mg/kg/day (exposure ratio > 7) showed renal hyaline droplet accumulation. This is also considered a species-specific response that is not relevant to humans (Hard et al. 1993[8]).

Genotoxicity

Macitentan was not mutagenic at up to 5 mg/plate in both the presence and absence of metabolic activation in standard *Salmonella typhimurium* strains. The rat liver S9 preparation was shown to generate ACT-080803 (present in excreta) and ACT-132577 (predominant metabolite in plasma). Macitentan was also negative in the mouse lymphoma L5178Y TK+/– assay at concentrations up to those inducing toxicity. Tests of in vitro (PHA-stimulated human lymphocytes) and in vivo (rat bone marrow micronucleus test) clastogenicity were also negative. The assays used and the conditions employed were consistent with the relevant EMA guideline (CPMP/ICH/141/95).

[4] Tripiciano A., Filippini A., Giustiniani Q. and Palombi F. 1996. Direct visualization of rat peritubular myoid cell contraction in response to endothelin. Biology of Reproduction, 55: 25–31

[5] Jones H.B., Macpherson A., Betton G.R., Davis A.S., Siddall R. and Greaves P. 2003. Endothelin antagonist-induced coronary and systemic arteritis in the beagle dog. Toxicologic Pathology, 31: 263–272.

[6] McDuffie J.E., Yu X., Sobocinski G., Song Y., Chupka J. and Albassam M. 2006. Acute coronary artery injury in dogs following administration of CI-1034, an endothelin A receptor antagonist. Cardiovascular Toxicology, **6**: 25–38.

[7] Vansell N.R. and Klaassen C.D. 2001. Increased biliary excretion of thyroxine by microsomal enzyme inducers. Toxicology and Applied Pharmacology, 176: 187–194.

[8] Hard G.C., Rodgers I.S., Baetcke K.R., Richards W.L., McGaughy R.E. and Valcovic L.R. 1993. Hazard evaluation of chemicals that cause accumulation of α_{2u}-globulin, hyaline droplet nephropathy, and tubule neoplasia in the kidneys of male rats. Environmental Health Perspectives, 99: 313–349.

Two macitentan metabolites, ACT-080803 and ACT-373898 (present in plasma and excreta), were also negative when tested in isolated form in Ames bacterial mutagenesis assays.

Carcinogenicity

Two-year carcinogenicity studies, conducted according to the relevant EMA guideline (CPMP/ICH/299/95), were performed using B6C3F1 mice and Wistar rats of both sexes given a daily oral dose of macitentan. In both studies, the high dose (HD) approximated the MTD for males, as indicated by clinical signs and effects on body weight, and exceeded the MTD for females. The HD produced exposure ratios of > 100 for both macitentan and for ACT-132577 in mice of both sexes, and ranged from 20 to 100 in rats. Macitentan showed no signals for oncogenic potential, consistent with its lack of activity in genotoxicity assays.

Reproductive toxicity

Macitentan was assessed for effects on fertility (both sexes), embryofetal development, and pre-/postnatal development in Wistar rats, and for effects on embryofetal development in rabbits. The scope and design of the studies were appropriate and consistent with the relevant EMA guideline (CPMP/ICH/386/95).

Table 4: Relative exposure[a]

Species	Study type (number)	Dose[b] (mg/kg/day)		AUC_{0-24h} (µg·h/mL)		Exposure ratio[c]	
				Macitentan	ACT-132577	Macitentan	ACT-132577
Rat (Wistar)	Embryofetal development (T-05.008)	150, 450[d]	♀	552, 726 (GD17)	477, 823 (GD17)	102, 134	31, 53
	Pre-/Postnatal development (T-09.617)	10, 50, 250	♀	69.1, 143, 294 (PND12)	69.8, 185, 375 (PND12)	13, 26, 54	4.5, 12, 24
	Juvenile development (T-11.001)	**3**, 10, 30	♂	**>3.9**, 16.8, 22.2 (PND69)	**>32.4**, 64.0, 121 (PND69)	**>0.7**, 3.1, 4.1	**2.1**, 4.1, 7.8
			♀	**32.9**, 53.4, 102 (PND69)	**34.9**, 66.7, 111 (PND69)	**6.1**, 9.9, 19	**2.2**, 4.3, 7.1

Species	Study type (number)	Dose[b] (mg/kg/day)		AUC_{0-24h} (µg·h/mL)		Exposure ratio[c]	
				Macitentan	ACT-132577	Macitentan	ACT-132577
Rabbit (NZW)	Embryofetal development (T-05.029)	2.5, 12.5, 25	♀	118, 323, 396 (GD19)	520, 2280, 4290 (GD19)	22, 60, 73	33, 147, 276
Human (healthy volunteers)	steady state– 10 days (D-06.044 (AC-055-102))	[10 mg]	♂	5.40	15.54	–	–

[a]All listed studies are GLP compliant; [b]doses given po (gavage); [c]animal:human plasma AUC $_{0-24h}$; [d]values at NOAEL dose for maternal toxicity are underlined and for juvenile toxicity are bolded and underlines (NOAEL values for embryofetal development were < LD). As indicated in the table, exposure ratios at maternal NOAEL doses, for both rat and rabbits, were > 50, however, embryofetal development was much more sensitive to the test article and NOAEL doses were not identified for either species.

Male rats treated for ≥ 10 weeks and female rats treated for ≥ three weeks with relatively high macitentan doses (NOAEL = 250 mg/kg/day) showed no effects on fertility. However, oral dosing of pregnant rats and rabbits with macitentan produced significant post-implantation loss and an increased incidence of mandibular arch fusion and cardiovascular abnormalities. For example, all rabbit fetuses from does dosed orally from GD6–GD19 at 12.5 mg/kg/day of macitentan showed mandibular arch fusion abnormalities and about a quarter showed cardiovascular abnormalities. It was concluded that macitentan is fetotoxic at high doses and teratogenic at all doses tested. The teratogenicity of macitentan is a known drug class effect for ET-1 receptor antagonists, which recapitulates effects seen in fetuses with gene knockouts of ET-1 or the ETA receptor, and may be due to inhibition of migration and/or proliferation of cranial neural crest cells (for example, Spence et al. 1999[9]). Placental transfer of macitentan was not examined; however, the lack of such data is of little consequence given the demonstrated teratogenicity of this drug.

Oral dosing of rats, from late pregnancy through lactation, at macitentan doses producing exposure ratios of approximately 10 or greater, produced significant increases in pup deaths, reduction in fertility of offspring, and histological changes in pups (including enlarged periportal hepatocytes, bile duct hyperplasia, and tubular atrophy of testis). Consistent with these findings, macitentan and its metabolites were shown to be excreted into milk by rats.

Pregnancy classification

The sponsor has proposed Pregnancy Category X. Category X covers 'drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy'. This category is appropriate given the experimental findings that macitentan is fetotoxic and teratogenic.

[9] Spence S., Anderson C., Cukierski M. and Patrick D. 1999. Teratogenic effects of the endothelin receptor antagonist L-753,037 in the rat. Reproductive Toxicology, 13: 15–29

Impurities

A repeat-dose toxicity study in rats suggested that the levels of two impurities in the drug substance/product were not of toxicological concern. All macitentan impurities were negative for genotoxic potential in the Ames assay using predictive computer programs, and the major impurity was confirmed as being negative in actual Ames assay testing.

Paediatric use

Macitentan is intended for use by persons of 12 years of age and over. The safety of macitentan use in young animals was tested by daily oral dosing of Wistar rats from PND4–69. The NOAEL dose from this study produced exposure ratios of approximately 6 or less for macitentan and about two for ACT-132577 (see 'juvenile development' study in Table 4 above). These values are not markedly different from those for more mature animals.

Phototoxicity

Macitentan contains two bromine-substituted moieties which may potentially undergo photocleavage reactions, raising the possibility of photosensitisation. Exposure of mouse Balb/c 3T3 fibroblasts to macitentan with or without ultraviolet-A irradiation produced a modest increase in phototoxicity. However, no evidence of photosensitisation was observed in an in vivo study in macitentan-treated hairless rats. The weight of evidence suggests that photosensitisation should not be an issue for macitentan-treated patients.

Nonclinical summary and conclusions

- The nonclinical studies presented were comprehensive and had no major deficiencies.
- Results of the primary pharmacology studies support the use of macitentan for the treatment of PAH.
- Secondary PD and safety pharmacology studies did not identify any unexpected clinical hazards.
- Drug interaction studies suggested that macitentan and its metabolites are unlikely to change the PK of co-administered drugs via inhibition of CYP enzyme metabolism or inhibition of the membrane transporter proteins.
- Target organs identified in repeat-dose toxicity studies included liver, haemopoietic system, testis, and vasculature.
- Liver effects were not of clinical concern as they were primarily adaptive in nature and only occurred at very high relative exposure margins. Moreover, neither macitentan nor its active metabolite inhibited bile salt transport.
- Dose-related, reversible decreases in haematocrit, RBC count and haemoglobin were observed in nonclinical studies and are a known clinical adverse effect of macitentan and other ERAs.
- Dog studies showed induction of multicentric arteritis/periarteritis in the heart and other organs at clinical exposure levels and extramural arterial intimal thickening at higher exposure levels. Endothelin antagonist-induced arteritis in dogs (not seen in rats or mice) has been well described in the literature and appears to be a species-specific effect. While the mechanism remains unclear, it is not associated with systemic vasodilation, hypotension, and reflex tachycardia that are easy to monitor in patients.
- The clinical relevance of the various observed effects of macitentan on the testicles and sperm in rats and dogs at relatively low exposure margins cannot be fully

excluded. The findings are appropriately summarised both in the nonclinical safety concern section of the Risk Management Plan (RMP) and in the "Male Fertility" section of the PI under Precautions.

- There was no evidence to suggest that macitentan poses a genotoxic or carcinogenic risk.
- Macitentan was teratogenic in animal models and was appropriately categorised as Pregnancy Category X.
- There are no nonclinical objections to the registration of macitentan.
- The drafts of the RMP and of the PI should be amended.

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.

Clinical rationale

PAH is characterised by vasculopathy and remodelling of the pulmonary circulation resulting in narrowing of the arterial lumen and impaired vasodilation. This leads to an increase in pulmonary arterial pressure and pulmonary vascular resistance, which limits the ability of the right ventricle to pump blood through the lungs and thus causing shortness of breath, and eventually resulting in right heart failure and death. According to the sponsor, the pathophysiology of PAH is not fully understood, but is thought to involve abnormal interactions between endothelial and smooth muscle cells, leading to vasoconstriction, vascular smooth muscle cell proliferation, vascular endothelial proliferation, and in-situ thrombosis. Mediators of these pathological changes include an up-regulated ET-1 system, defective prostacyclin synthase activity, and abnormalities of the nitric oxide pathway. Current pharmacological therapies for PAH are therefore targeted towards these three mediator pathways: ERAs which inhibit the effects of elevated ET-1 levels and thus reducing vasoconstriction, smooth muscle cell proliferation and pulmonary vessel fibrosis; prostacyclin analogs which relax and reduce proliferation of vascular smooth muscle cells; and PDE-5 inhibitors which potentiate the anti-platelet, anti-proliferative, and vasodilatory effects of nitric oxide.

According to the sponsor, medications currently approved for the treatment of PAH have mainly shown benefits in terms of symptom relief, which were evaluated mostly as improvement in exercise capacity in relatively short-term, placebo-controlled studies in selected populations. Long-term clinical outcome (morbidity and mortality) had not been investigated as primary endpoints in controlled trials beyond three to six months of treatment. The sponsor was therefore of the opinion that there was an unmet medical need in the availability of a pharmacological agent with demonstrated benefit for long-term clinical outcome (morbidity and mortality) in patients with PAH. In addition, the sponsor was of the opinion that macitentan could have potentially better efficacy and safety characteristics compared to currently approved ERAs, in view of its high affinity and sustained occupancy of endothelin receptors, and PK characteristics consistent with once-daily dosing.

> Comments: The clinical rationale is sound. The currently approved ERAs for the treatment of PAH in Australia are bosentan and ambrisentan. Bosentan has a recommended dosing regimen of 125 mg twice daily per oral, and is approved for the indications for 'the treatment of

- idiopathic PAH

- familial PAH
- PAH associated with scleroderma or
- PAH associated with congenital systemic to pulmonary shunts including Eisenmenger's physiology in patients with WHO Functional Class (FC) II, III or IV symptoms'[10]

Ambrisentan has a dosing regimen of 5 mg once daily per oral, and is approved for the indications for 'the treatment of:

- idiopathic PAH,
- PAH associated with connective tissue disease (PAH-CTD), in patients with WHO FC II, III or IV symptoms'[11]

The primary endpoint of the registration Phase III trials for bosentan as well as for ambrisentan, as described in their respective Australian PI, was change from baseline in the six-minute walk distance at 12 weeks (that is, a measure of improvement in exercise capacity).

Contents of the clinical dossier

The submission contained the following clinical information:

- 14 clinical pharmacology studies, including 12 that provided PK data and two that provided pharmacodynamic (PD) data.
- one population PK (PopPK) analysis (sub-study of Study AC-055-302).
- one pivotal efficacy/safety study (SERAPHIN study [AC-055-302]).
- one dose-finding study (Study AC-055-201)
- one other efficacy/safety study (MUSIC study [AC-055B201]).

In this evaluation report, Study AC-055-302 (conducted in a PAH patient population) will be evaluated as the pivotal efficacy/safety study, and Study AC-055-201 (conducted in essential hypertension patient population) as a dose-finding study. As per instructions in the TGA's 'statement of requirements', Study AC-055B201 will be evaluated for safety only.

Paediatric data

The submission included paediatric efficacy/safety data, as this application is for the use of macitentan in patients aged 12 years and older. Paediatric efficacy/safety data is only available for the pivotal Study (AC-055-302) which enrolled subjects aged 12 years and above. All other clinical studies submitted in this application did not include any paediatric data.

Good clinical practice

The clinical studies reviewed in this evaluation were in compliance with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice.

[10] Australian PI for Bosentan, April 2011
[11] Australian PI for Ambrisentan, October 2012

Pharmacokinetics

Studies providing pharmacokinetic data

Table 5 (below) shows the studies relating to each PK topic and the location of each study summary.

Table 5: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	Primary Aim of the Study
PK in healthy adults	General PK-Single dose	AC-055-101	To evaluate the tolerability and safety, and PK and PD of single ascending doses of macitentan (0.2, 1, 5, 25, 100, 300, or 600 mg capsule)
		AC-055-109	To evaluate the tolerability and safety, and relative PK properties of macitentan in Japanese versus Caucasian healthy subjects after single-dose treatment (10 mg tablet)
		AC-055-104	To investigate the rate and routes of excretion of macitentan, and the mass balance in urine and faeces, the PK of total radioactivity in blood and plasma, the PK of macitentan and its metabolites in plasma, and to identify and quantify the macitentan metabolites in plasma, urine, and faeces, with a single oral dose of 10 mg 14C-labeled macitentan capsule
	- Multi-dose	AC-055-102	To evaluate the tolerability and safety, and PK and PD of multiple ascending doses of macitentan (1, 3, 10, or 30 mg capsule qd for 10 days)
	Bioequivalence † - Single dose	AC-055-108	To evaluate the PK properties, and the tolerability and safety of the 10 mg tablet and 10 mg capsule formulations of macitentan after single-dose treatment
	Food effect	AC-055-103	To evaluate the effect of food on the PK of single dose of macitentan 10 mg capsule
PK in special populations	Hepatic impairment	AC-055-110	To assess the effect of mild, moderate, or severe hepatic impairment due to liver cirrhosis on the PK of macitentan and its metabolites, following a single oral dose of

PK topic	Subtopic	Study ID	Primary Aim of the Study
			macitentan 10 mg tablet
	Renal impairment	AC-055-112	To evaluate the PK properties of a single oral dose of macitentan (10 mg tablet) in subjects with severely impaired renal function compared to matched healthy subjects
PK interactions	Warfarin	AC-055-105	To evaluate the effect of multiple-dose treatment with macitentan on the PK and PD of a single dose of warfarin
	Sildenafil	AC-055-106	To evaluate the effect of macitentan on the PK of sildenafil and its desmethyl metabolite at steady state, and to evaluate the effect of sildenafil on the PK of macitentan and its metabolite, ACT-132577, at steady state
	Ketoconazole	AC-055-107	To evaluate the influence of concomitant ketoconazole on the PK of macitentan and its metabolite, ACT-132577
	Cyclosporin A, Rifampicin	AC-055-111	To evaluate the effect of multiple-dose treatment with cyclosporin A on the PK of multiple-dose macitentan and its metabolites (Part A), and to evaluate the effect of multiple-dose treatment with rifampicin on the PK of multiple-dose macitentan and its metabolites (Part B)
Population PK analyses	Target population	AC-055-302 PK/PD	To characterise the relationship between macitentan exposure and different cardiac haemodynamic parameters, the 6-minute walk distance, and other efficacy and safety endpoints

† Bioequivalence of different formulations.
qd = once daily

Evaluator's summary and overall conclusions on pharmacokinetics

Overall, the PK data is adequate with respect to evaluation of this application. ACT-064992 is an orally active, non-peptide, dual endothelin ET_A and ET_B receptor antagonist (ERA). T_{max} was found to be about eight hours after drug administration, and apparent elimination half-life (t½) of approximately 16 hours. Macitentan parent drug was metabolised to its active metabolite ACT-132577, a reaction which had been found in vitro studies to be mediated by the cytochrome P450 system, mainly CYP3A4 with a minor contribution of CYP2C19. ACT-132577 was found to be formed slowly, with a T_{max} of 24 hours post-dose in multiple-dosing, and was eliminated with a t½ of approximately 48 hours. After multiple dosing, steady-state conditions of macitentan and ACT-132577 were obtained after three days and seven days. The exposures of macitentan and ACT-132577

were comparable when macitentan was administered in the fasted or in the fed states. Macitentan and its circulating metabolites were found to be highly bound (≥ 99%) to plasma proteins in humans. Macitentan was found to be extensively metabolised before excretion, and no unchanged macitentan parent drug or the active metabolite ACT-132577 was recovered from urine in a radiolabel mass balance study. Renal excretion of macitentan metabolites was found to be the most important route of elimination. Overall, the PK results are consistent with a once-a-day dosing regimen.

A PopPK/PD modelling analysis (Study AC-055-302 PK/PD) on the target study population showed that macitentan trough plasma concentrations (used as a surrogate for exposure) for both the 3 mg and 10 mg dose groups were higher than those observed in healthy subjects in Study AC-055-102 (3 mg dose: 1.6 to 1.9 times higher; 10 mg dose: 1.6 to 2.3 times higher). ACT-132577 plasma concentrations were also higher in Study AC-055-302 PK/PD than those observed in healthy subjects (3 mg dose: 1.2 to 1.5 times higher; 10 mg dose: 1.5 times higher).

Analyses of the PK of macitentan and its metabolites in healthy subjects and in subjects with mild, moderate and severe hepatic impairment, showed that $AUC_{0-\infty}$ and C_{max} of macitentan parent drug and its active metabolite, ACT-132577, were lower in all three groups of subjects with hepatic impairment compared to healthy subjects. For macitentan parent drug, $AUC_{0-\infty}$ in the hepatic impaired groups was 66% to 94% that of the healthy group, while C_{max} was 52% to 81% that of the healthy group. For ACT-132577, $AUC_{0-\infty}$ was 74% to 81% that of the healthy group, while C_{max} was 74% to 79% that of the healthy group. There was no particular trend noted in these PK parameters with increasing severity of hepatic impairment. Overall, these lower $AUC_{0-\infty}$ and C_{max} of macitentan and its metabolite in subjects with hepatic impairment compared to healthy subjects were not considered to be of a magnitude that would warrant dose adjustments in subjects with hepatic impairment.

Analyses of the PK of macitentan and its metabolites in healthy subjects and in subjects with severe renal function impairment (SRFI) showed that $AUC_{0-\infty}$ and C_{max} of macitentan parent drug and its active metabolite, ACT-132577, were higher in subjects with SRFI compared to healthy subjects ($AUC_{0-\infty}$: 24% and 58% higher for macitentan and ACT-132577; C_{max}: 11% and 39% higher). Overall, these higher $AUC_{0-\infty}$ and C_{max} of macitentan and ACT-132577 in SRFI subjects compared to healthy subjects were not considered to be of a magnitude that would warrant dose reduction in subjects with SRFI.

Drug-drug interaction (DDI) studies investigating potential DDI of macitentan with warfarin (commonly administered to PAH patients, and metabolised by a range of CYPs), sildenafil (CYP3A4 substrate and approved for treatment of PAH), ketoconazole (potent inhibitor of CYP3A4), cyclosporine A (inhibitor of CYP3A4 and of the uptake transporters) and rifampicin (potent inducer of CYP3A4) were conducted. Results showed that there was no clinically relevant DDI with warfarin, sildenafil, ketoconazole and cyclosporine. Co-administration of rifampicin with macitentan decreased the exposure to macitentan parent drug significantly (geometric means of AUC_{τ} and C_{trough} were 79% and 93% lower) but did not change the exposure to the active metabolite, ACT-132577 to a clinically relevant extent, leading to the conclusion that reduced efficacy of macitentan in the presence of rifampicin should be considered.

In the current application, absolute bioavailability studies as well as studies to establish that the proposed formulation is optimal (for example, a study on bioavailability relative to an oral solution of the drug) have not been submitted. As previously described, the sponsor had provided the reasons for these omissions. The sponsor had stated that as macitentan has very low solubility (≤ 1 μg/mL) and poor stability in aqueous media at physiological pH, attempts to develop an IV formulation for human use had failed despite exploration of several potential solvent systems. Hence, in lieu of absolute bioavailability studies, the bioavailability of macitentan was simulated using a physiologically-based PK

computer model. This justification for the lack of absolute bioavailability studies is considered by the evaluator to be reasonable. With regards to the lack of a study on bioavailability relative to an oral solution of the drug, the sponsor had stated that the technical feasibility and stability of an oral solution of macitentan had been investigated, but that the low solubility of macitentan in various aqueous media at physiological pH had made it challenging to achieve an oral solution. None of the systems investigated were found to be suitable for developing an oral solution due to issues with solubility and/or stability, leading the sponsor to conclude that the development of an oral solution formulation was not feasible due to the physicochemical characteristics of the compound. This justification for the lack of a study on bioavailability relative to an oral solution of the drug is considered by the evaluator to be reasonable.

The PK information in the PI is satisfactory.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 6 (below) shows the studies relating to each PD topic.

Table 6: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	Primary Aim of the Study
Secondary Pharmacology	Effect on sperm concentration	AC-055-113	To demonstrate that treatment with macitentan 10 mg tablet once daily over 12 weeks does not lead to a clinically relevant decrease in sperm concentration, and to investigate the effect of macitentan on sperm quality and on serum concentrations of hormones of the HPA and HPG axes, in healthy male subjects
	Effect on cardiac repolarisation (thorough QT study)	AC-055-114	To demonstrate that macitentan does not have an effect on cardiac repolarisation exceeding the threshold of regulatory concern, as measured by the QTc interval after repeated administration of oral daily doses of 10 mg and 30 mg tablets.
Population PD and PK-PD analyses	Target population	AC-055-302 PK/PD	To characterise the relationship between macitentan exposure and different cardiac haemodynamic parameters, the 6-minute walk distance, and other efficacy and safety endpoints

Evaluator's summary and overall conclusions on pharmacodynamics data

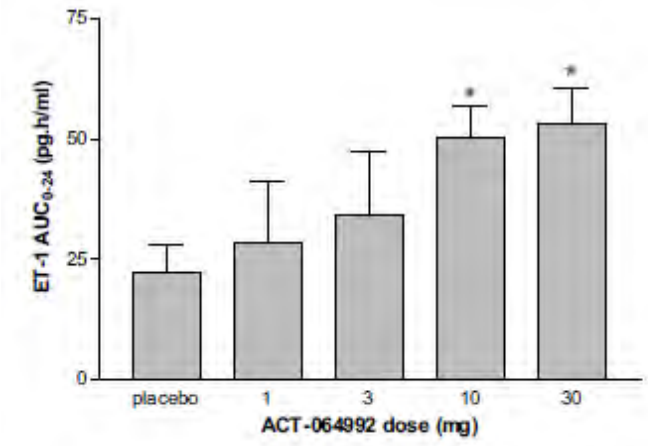
Overall, the PD data is adequate with respect to evaluation of this application. The SAD and MAD Studies showed PD effect at the ET receptor level. After multiple dosing, at steady-state, there was a dose-dependent increase in plasma ET-1 concentrations from 1 to 10 mg, with no further increase beyond the 10 mg once daily dose, indicating full receptor blockade at this dose level. PD effect on systemic BP was investigated in Study AC-055-201, and results showed a dose-related decrease in sitting diastolic BP (SiDBP) from baseline to Week 8, and the decrease which was statistically significant versus placebo for macitentan 10 mg once daily dose, but not for macitentan 3 mg once daily dose. Analysis of the relationship between macitentan/ACT-132577 concentrations and change from baseline in SiDBP indicated that the 10 mg dose appeared to be close to the plateau of the pharmacological effect.

Dosage selection for the pivotal studies

No dedicated dose-finding study was conducted in patients with PAH. The sponsor had stated that their strategy was to employ PD data on ET-1 levels and haemodynamic efficacy data on BP reduction in patients with mild to moderate essential hypertension to determine the dose range to be tested in the Phase III study in patients with PAH. Through the inhibitory effect on ET-1 receptors, ERAs lead to an increase in plasma ET-1 levels and a decrease in systemic BP, both of which can hence be used as biomarkers of pharmacological effect. The sponsor had stated that their strategy was based on the assumption that a dose shown to be efficacious in systemic hypertension would also be haemodynamically effective in PAH, as was previously observed with the ERA bosentan.

In the MAD Study (AC-055-102) in healthy subjects, a dose-dependent increase in ET-1 levels was observed from 1 to 10 mg of macitentan, with no further increase beyond the 10 mg once daily dose (Figure 5) suggesting that this dose provided maximum inhibition of the ET receptor and was thus a likely ceiling for cardiovascular effects related to ET-receptor antagonism. In addition, a statistically significant difference in ET-1 levels compared to the placebo group was observed in the 10 mg and 30 mg dose groups but not in the 3 mg or 1 mg dose groups.

Figure 5: Effect of macitentan (ACT- 064992) on plasma ET-1 concentrations on Day 10, Study AC-055-102

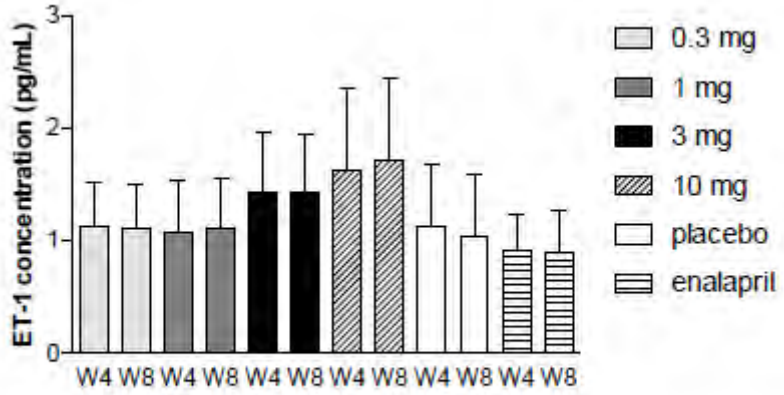


Each bar represents the arithmetic mean and SD. N = 6 for the different ACT-064992 doses and N = 8 for the placebo group.
*p <0.05 when compared to placebo (derived by exploratory statistical analyses)

These results were supported by the results of Study AC-055-201 in patients with essential hypertension, where only a marginal effect on ET-1 concentration was observed

in the 0.3 and 1 mg macitentan dose groups, while a more marked effect on ET-1 was observed in the 3 and 10 mg macitentan dose groups (Figure 6).

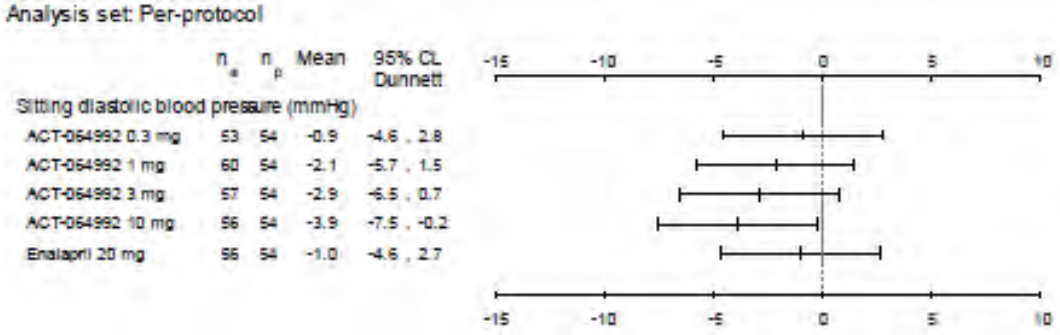
Figure 6: Plasma ET-1 concentrations (pg/mL) (mean and SD) at Weeks 4 and 8, Study AC-055-201



W4 = Week 4; W8 = Week 8.
ET-1 = endothelin-1; SD = standard deviation.

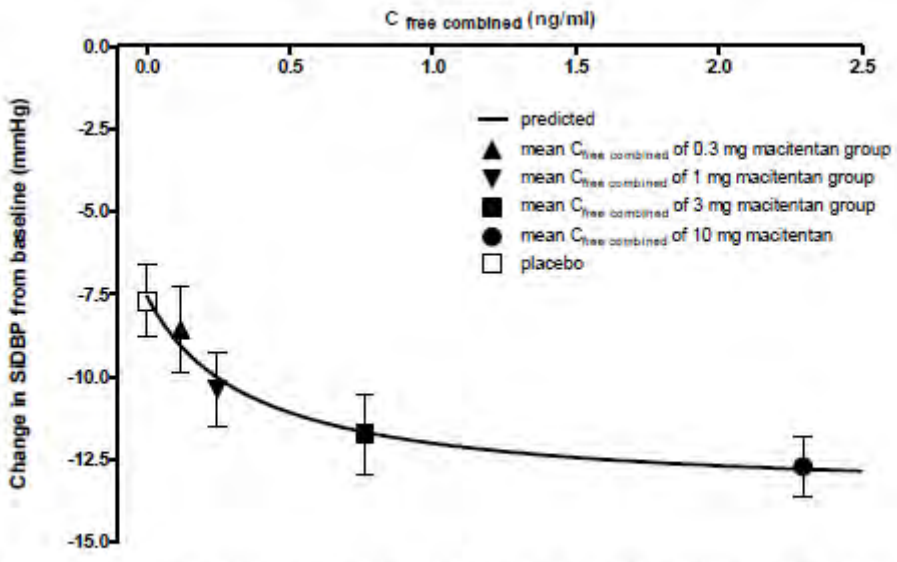
In terms of the effect of macitentan on systemic BP as a biomarker of pharmacological effect, in Study AC-055-201, the reduction in trough SiDBP from baseline was statistically significant when compared to placebo only for macitentan 10 mg, but not for 3 mg, 1 mg or 0.3 mg, although the mean reduction in trough SiDBP from baseline observed in the 3 mg dose group was considered clinically relevant (Figure 7).

Figure 7: Change in sitting diastolic blood pressure from baseline to end of Period II (Placebo-corrected), Study AC-055-201



Similar results were observed in the endpoint of change from baseline to Week 8 in mean trough SiSBP, with statistically significant reduction from baseline in trough SiSBP compared to placebo only in the macitentan 10 mg dose. In addition, PK/PD analysis results of study AC-055-201 showed that macitentan 10 mg appeared to be at or near the plateau of maximal haemodynamic efficacy (Figure 8).

Figure 8: PK/PD analysis: Change in SiDBP (mmHg) (mean ± SEM) versus $C_{free\ combined}$ (ng/mL)[12] (mean ± SEM) at Week 8 including predicted data, Study AC-055-201



$C_{free\ combined}$ = free combined plasma concentration; SEM = standard error of mean; SiDBP = sitting diastolic blood pressure.

Based on these results, the sponsor had decided to use 10 mg once daily as the dose to be tested in the pivotal Phase III study in PAH. In addition, a lower dose of 3 mg once daily was also tested in the pivotal Phase III study in PAH, as 3 mg dose was considered to correspond to the lowest dose showing any signal of relevant hemodynamic efficacy in the study in subjects with essential hypertension.

> Comments: The rationale for the dose selection for the pivotal Phase III trial is sound.

Efficacy

Pivotal efficacy studies

Study SERAPHIN (AC-055-302)

For the proposed indication of long-term treatment of PAH in patients of WHO FC II to IV

AC-055-302 was a multi-centre, randomised, double-blind, placebo-controlled, parallel-group, event-driven, Phase III study evaluating the effects of macitentan on morbidity and mortality in subjects with symptomatic PAH. Subjects were randomised in a 1:1:1 ratio to one of three treatment groups (3 mg macitentan, 10 mg macitentan or matching placebo once daily). The study included a screening period (up to 28 days) followed by a treatment period from randomisation to the end-of-treatment (EOT) visit. End-of-study (EOS) occurred when the target of 285 events confirmed by the Clinical Event Committee (CEC) was expected to have been achieved. The EOT visit either coincided with the EOS visit for subjects who were still on study treatment or occurred earlier in cases of premature discontinuation of study drug. Subjects who prematurely discontinued double-blind study

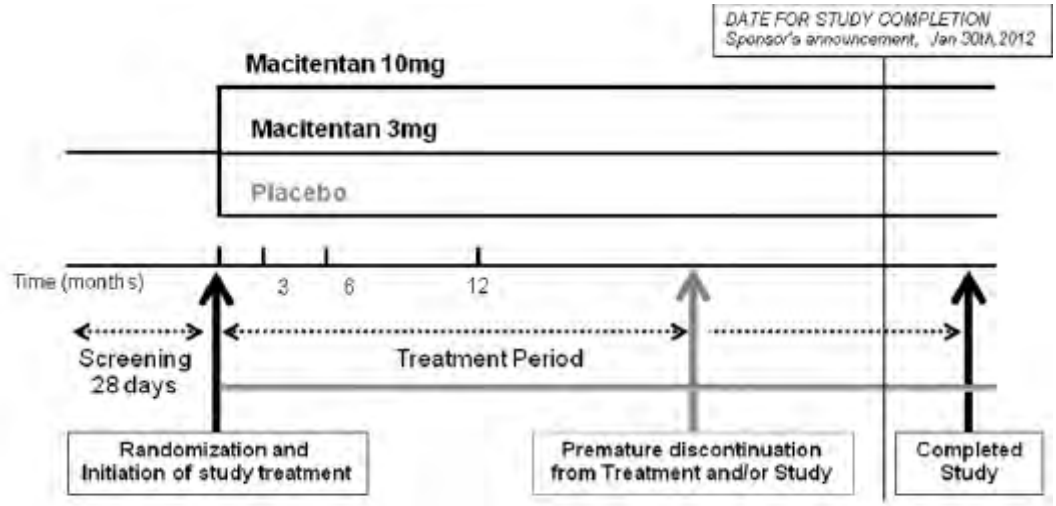
[12] In order to account for the contribution of ACT-132577 to the effect on SiDBP, a concentration parameter for the combined unbound fraction ($C_{free\ combined}$) was derived from the C_{trough} concentrations of macitentan and ACT-132577 using the formula: $C_{free\ combined}$ = (0.4/100) *C_{trough} macitentan + (0.5/100) *0.2 C_{trough} ACT-132577. This formula assumed that the free fractions of macitentan and ACT-132577, as determined in vitro, were 0.4% and 0.5%, and that ACT-132577 was approximately 8-fold less potent in vitro than macitentan on ET_A and 2-fold less potent on ET_B

treatment due to clinical worsening of PAH and obtained written approval from the sponsor, and subjects who completed the study as scheduled, could enter the open-label extension study, SERAPHIN OL. For subjects who had opted not to participate or who were not eligible to participate in SERAPHIN OL, a 28-day safety follow-up after EOT was performed. A schema of the study design is presented in Figure 9. The clinical study report (CSR) submitted for this application presents only the results for the double-blind phase.

The primary objective of the study was to demonstrate that either dose of macitentan (3 mg or 10 mg) reduced the risk of morbidity and mortality in subjects with symptomatic PAH. The secondary objectives of the study were to demonstrate that either dose of macitentan improved exercise capacity or WHO FC, or reduced the risk of death due to PAH or hospitalisation for PAH up to EOT in subjects with symptomatic PAH, to demonstrate that either dose of macitentan reduced the risk of death of all causes up to EOT and up to EOS, and to evaluate the safety and tolerability of macitentan in subjects with symptomatic PAH.

This was a multi-centre study where subjects were enrolled in a total of 158 centres in 39 countries across Africa, Australia, Asia, Europe, Latin America, and North America. The study's start and end dates were 25 May 2008 and15 March 2012.

Figure 9: Study design, Study AC-055-302



End of Treatment (EOT) is the date of discontinuation from treatment. Patients could discontinue study treatment at any time following randomization. EOT coincided with the end of study for patients who were ongoing on study drug on the date of study completion (30 January 2012 announced by Actelion).

End of study (EOS) is the date of discontinuation from study.

Study completers are patients who were still in the study (alive and available for a visit/ to be contacted) on the date of study completion, independent of whether or not the patients had discontinued the study prematurely or had been enrolled into the SERAPHIN open label study following a morbidity event.

Other efficacy studies

Study AC-055-201

Study AC-055-201 was a double-blind, randomised, placebo and active-controlled study to evaluate the efficacy, safety and tolerability of macitentan in subjects with mild to moderate essential hypertension. The primary objective was to evaluate the effect of a once-daily oral regimen of four doses of macitentan (0.3 mg, 1 mg, 3 mg and 10 mg) on SiDBP at trough after eight weeks of treatment. Secondary objectives were to evaluate the effect of a once-daily oral regimen of the four doses of macitentan on control/response rate on SiDBP, and on sitting systolic BP (SiSBP) at trough at eight weeks and its

control/response rate, as well as to evaluate the safety and tolerability of macitentan. This was a multi-centre (17 centres in Israel and five centres in Serbia), double-blind, randomised, placebo- and active-controlled, parallel group, dose-ranging study.

Evaluator's summary and overall conclusions on efficacy

Overall, the study design, study inclusion and exclusion criteria, and study endpoints of the pivotal Phase III Study (AC-055-302) were appropriate and in line with the recommendations of the TGA-adopted EMA guidelines on the clinical investigation of medicinal products for the treatment of PAH. The study primary endpoint allowed evaluation of all-cause mortality and PAH-related morbidity, while the study secondary endpoints of change from baseline in six minutes' walk distance (6MWD) and the WHO FC allowed evaluation of the effect of macitentan on exercise capacity and clinical symptoms. Baseline demographic and disease characteristics were comparable among treatment groups, and were generally consistent with the target patient population. The majority of subjects (63.7%) had concomitant PAH therapy at baseline, of which sildenafil was the commonest, taken by 57.6% of the overall study population. The commonest type of concomitant PAH therapy was PDE-5 inhibitors, taken by 61% of the overall study population. It was noted, however, that the sample size of adolescent subjects (12 to < 18 years old) was very small (N=20) as was the group of subjects with baseline WHO FC IV (N=14).

Analysis of the primary efficacy endpoint (that is, time to first morbidity or mortality event up to EOT) showed that the hazard ratio versus placebo for the first occurrence of a morbidity or mortality event was 0.704 ($p = 0.0108$) with the macitentan 3 mg, and 0.547 ($p < 0.0001$) with macitentan 10 mg. This gives relative risk reductions for the occurrence of a morbidity or mortality event of 30% and 45% with macitentan 3 mg and10 mg compared to placebo. The treatment effect with the 10 mg dose met the pre-specified significance criteria for a 'conclusive study' (that is, $p<0.005$). The treatment effect with the 3 mg dose did not meet the pre-specified significance criteria for a 'conclusive study', but satisfied that for a 'positive study' (that is, $p<0.025$). The Kaplan-Meier curves of the first morbidity or mortality event showed that the treatment effect of the two macitentan doses on the primary endpoint appeared to be established early, with the separation in the curves between the macitentan groups and the placebo group observed by Month 6, and was sustained for the duration of the study. Analysis of the primary endpoint in the per-protocol set and other sensitivity analyses of the primary endpoint (based on variation of the endpoint definition and/or population analysed) yielded results consistent with those of the main analysis in the all-randomised set.

Subgroup analyses of the primary endpoint across subgroups of gender (male versus female), race (White versus Asian versus Others), concomitant PAH therapy at baseline (yes versus no), PAH aetiology at baseline (idiopathic, familial, HIV infection, drugs and toxins versus collagen vascular disease versus congenital shunts), geographical region (North-America versus Western Europe/Israel versus Eastern Europe/Turkey versus Asia versus Latin America), age (< 18 versus 18 to 64 versus > 64 years), baseline WHO FC (WHO FC I–II versus III–IV) and baseline 6MWD (6MWD > versus ≤ 380 m) yielded results that were generally consistent with those in the overall study population, but was less so with macitentan 3 mg than with macitentan 10 mg, in particular in subgroups that included subjects with or without background PAH therapy, and baseline WHO FC I/II versus III/IV. The p-values for the interaction test did not show heterogeneity of the treatment effect (macitentan versus placebo) across the subgroups.

Overall, the proportion of subjects with a confirmed primary endpoint morbidity or mortality event (that is, composite endpoint) was 38.0% and 31.4% in the macitentan 3 mg and 10 mg groups, compared with 46.4% in the placebo group. Analysis of the components of the primary endpoints showed that the commonest first-reported

morbidity or mortality event in all treatment groups was 'Other worsening of PAH' (28.8% and 24.4 % in the macitentan 3 mg and10 mg groups, versus 37.2% in the placebo group), followed by 'Death' (that is, all-cause deaths; 8.4% and 6.6% versus 6.8%). Competing risks analysis to explore the treatment effect on the morbidity component of the primary endpoint showed that subjects in the macitentan groups had a statistically significantly lower risk of disease worsening than subjects in the placebo group (p=0.0047 for macitentan 3 mg; p<0.0001 for macitentan 10 mg), but no statistically significant difference was observed between the macitentan and placebo groups for the risk of death (p=0.59 for macitentan 3 mg; p=0.79 for macitentan 10 mg). However, interpretation of these results needs to take into consideration the relatively lower incidence of mortality across all treatment groups, as compared to incidence of morbidity.

Analysis of the secondary endpoint of time to death due to PAH or hospitalisation for PAH up to EOT showed a relative risk reduction versus placebo in this endpoint of 33% with macitentan 3 mg (hazard ratio: 0.669; p = 0.0146), and of 50% with macitentan 10 mg (hazard ratio: 0.500; p<0.0001). Due to the hierarchical method of statistical analysis and as the endpoint of change from baseline in WHO FC yielded a p-value > 0.025 for macitentan 3mg, no confirmatory claims could therefore be made for the treatment effect observed for macitentan 3mg for this endpoint of time to death due to PAH or hospitalisation for PAH up to EOT.

As the endpoints of change from baseline in 6MWD and in WHO FC both yielded a p-values >0.005 but <0.025 for macitentan 10mg, the treatment effect with the 10 mg dose for this endpoint of time to death due to PAH or hospitalisation for PAH up to EOT could only be considered to satisfy the significance criterion for a 'positive study', but not a 'conclusive study'.

Analyses of other death-related secondary and exploratory endpoints (time to death of all causes up to EOT, time to death of all causes up to EOS, time to death due to PAH up to EOT [post-hoc analysis], and time to death due to PAH up to EOS) showed that there were no statistically significant difference in relative risk reductions of these mortality endpoints in both macitentan dose groups (3 mg and 10mg) compared to placebo. However, the study was not powered for these endpoints.

Analyses of the effect of macitentan on exercise capacity in terms of the 6MWD showed that after six months of treatment, the placebo-corrected mean change (SD) from baseline in 6MWD was 16.8 m (96.95) and 22.0 m (92.58) in the macitentan 3 mg and10 mg groups. The placebo-corrected median change from baseline to Month 6 in 6MWD was 14.0 m (p=0.0122) and 15.0 m (p=0.0078) in the macitentan 3 mg and 10 mg groups. The treatment effect with both the 3 mg and 10 mg doses did not meet the pre-specified significance criteria for a 'conclusive study' (that is, p<0.005), but satisfied that for a 'positive study' (that is, p<0.025). A repeated measures analysis for the change in 6MWD from baseline suggested that the treatment effect of macitentan (versus placebo) on the 6MWD was sustained over time up to Month 12. The estimated treatment effect over 12 months compared to placebo was 21.5 m (p=0.0003) and 25.4 m (p<0.0001) for macitentan 3 mg and10 mg. The odds ratio versus placebo for achievement or maintenance of 6MWD ≥ 380 m, remained above 1 up to Month 24 for macitentan 3 mg and10 mg (except at Month 18 for macitentan 3 mg, where the odds ratio was 0.997). The results of an ANCOVA Model adjusted for baseline 6MWD values, baseline WHO FC, and concomitant PAH therapy at baseline showed that there was a statistically significant treatment effect on change from baseline to Month 6 in 6MWD with macitentan 3mg and 10 mg in subjects who were in WHO FC III or IV at baseline, and with macitentan 10 mg in subjects who were on concomitant PAH therapy at baseline.

Analyses of the effect of macitentan on symptom relief in terms of improvements in WHO FC from baseline to Month 6 showed that there was a 54% and 74% higher chance relative to placebo of WHO FC improvement at Month 6 for subjects on the macitentan 3 mg and

10 mg, (p=0.0395 and p=0.0063). The treatment effect with the 10 mg dose did not meet the pre-specified significance criteria for a 'conclusive study' (that is, p<0.005), but satisfied that for a 'positive study' (that is, p<0.025). The treatment effect with the 3 mg dose did not meet either pre-specified significance criterion. At all visits up to Month 30, there was a greater proportion of subjects in the macitentan groups who had improvements in WHO FC compared to the placebo group, and a greater proportion in the macitentan 10 mg group compared to the 3 mg group. Analyses of the effect of macitentan on symptom relief in terms of change in Borg dyspnoea index from baseline showed that the estimated treatment effect over 12 months compared to placebo was -0.47 (p=0.0002) for macitentan 3 mg, and -0.38 (p=0.0029) for macitentan 10 mg.

Analyses of the effect of macitentan on quality of life showed that there was a statistically significant mean change from baseline (improvement) to Month 6, across all SF-36 questionnaire domains with the exception of the general health perception domain, for both macitentan doses. Analyses of pharmacoeconomic endpoints showed that compared to placebo, treatment with macitentan reduced the number of hospitalisation days per year (mean all-cause hospitalisation days per year: 7.5 and 5.7 days with macitentan 3 mg and 10 mg, versus 12.2 days with placebo; mean PAH-related hospitalisation days per year: 4.0 and 3.8 days, versus 8.3 days) and the number of hospitalisations per year (mean number of all-cause hospitalisations per year: 0.6 and 0.5, versus 1.0; mean number of PAH-related hospitalisations per year: 0.3 and 0.3 versus 0.7).

Although two doses of macitentan were tested in this pivotal Phase III study, the recommended dose for the proposed indication for treatment of PAH was 10 mg once daily. The efficacy results supported this dose selection. With regards to the primary efficacy endpoint, there was a greater reduction in the risk of occurrence of a morbidity or mortality event with macitentan 10 mg dose (45% risk reduction compared to placebo), compared with the 3 mg dose (30% risk reduction compared to placebo), and associated with a higher degree of statistical significance. In addition, only macitentan 10 mg showed a consistent treatment effect across subgroups of subjects with versus without background PAH therapy, and those with baseline WHO FC I/II versus III/IV. Although results for death-related endpoints showed no statistically significant difference between placebo and both macitentan doses, analysis of the secondary endpoint of time to death due to PAH or hospitalisation for PAH up to EOT showed a relative risk reduction versus placebo in this endpoint of 50% with macitentan 10 mg, with a level of statistical significance considered as a 'positive study' although not a 'conclusive study'. Although there was a relative risk reduction versus placebo in this endpoint of 33% with macitentan 3 mg, the level of statistical significance was such that no confirmatory claims could be made for this treatment effect (that is, it is to be considered descriptive). Analyses of the effect of macitentan on exercise capacity and symptom relief also yielded results showing greater effect for the 10 mg dose compared to the 3 mg dose (placebo-corrected mean change [SD] from baseline in 6MWD: 22.0 m [92.58] versus 16.8 m [96.95]; WHO FC improvement at Month 6: 74% [p=0.0063] versus 54% [p=0.0395; that is, not statistically significant] higher chance relative to placebo of WHO FC improvement at Month 6).

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy study (Study AC-055-302)

In the pivotal efficacy study, the following safety data were collected:

- General adverse events (AEs)

  The occurrence of AEs was checked at every visit throughout the study. All AEs occurring up to 28 days after EOT were reported in the CRF.

- AEs of particular interest

  In this study, AEs that had been reported with other ERAs were explored as AEs of special interest. These included groupings of 'liver disorders and abnormal liver function', 'haemoglobin decrease', 'oedema' and 'hypotension'. The preferred terms (PT) in these groupings were pre-specified prior to unblinding[13].

- Laboratory tests included haematology, and serum chemistry and liver function tests (including aminotransferases [ALT and AST], alkaline phosphatase [ALP], total bilirubin [TBIL] and direct bilirubin [DBIL], creatinine, urea, glucose, sodium, potassium and albumin). With the exception of ALT and AST, all haematology and clinical chemistry variables were measured at screening, Month 3, Month 6 and every six months until the EOT/event visit. ALT and AST were measured at screening and at monthly intervals after initiation of study treatment until at least 28 days after the EOT. If ALT and AST elevations exceeded three times ULN, a repeat confirmatory measurement was to be performed along with measurements of TBIL, DBIL and ALP. If confirmed, treatment was to be interrupted and ALT, AST, bilirubin and ALP were to be monitored every week after study drug interruption until the values returned to pre-treatment levels. Re-introduction of study treatment could be considered only if the potential benefits of treatment with study treatment outweighed the potential risks and when liver aminotransferase values were within the pre-treatment levels. In addition, the interruptions were required to be of less than four weeks' duration. Interruptions lasting for a longer period led to permanent discontinuation of study drug. The levels of ALT and AST had to be checked within three days after re-introduction, and at Week 2, and thereafter at monthly intervals. In addition, study drug was required to be permanently discontinued if ALT and/or AST > three times ULN and associated with clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue, flu-like syndrome), ALT and/or AST > three times ULN and TBIL ≥ two times ULN, or ALT and/or AST > eight times ULN. In women of childbearing potential, serum pregnancy tests were to be performed monthly from screening up to at least 28 days after EOT.

- Other safety variables included vital signs (BP and pulse rate), 12-lead electrocardiogram (ECG) and body weight measurements. Vital signs and body weight were recorded at screening, randomisation, Month 3, Month 6, every 6 months

[13] For the grouping of 'liver disorders and abnormal liver function', PTs from the overall AE list were included in this grouping if they appeared in the standardised MedDRA queries (SMQ) of 'drug-related hepatic disorders'. PTs included in this grouping were alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, bilirubin conjugated increased, blood alkaline phosphatase (ALP) increased, blood bilirubin increased, gamma-glutamyltransferase (GGT) increased, hepatic cirrhosis, hepatic enzyme increased, hepatic function abnormal, hepatitis, hepatitis acute, hyperbilirubinaemia, ischaemic hepatitis, jaundice, liver function test abnormal, liver injury, and transaminases increased. For the grouping of 'haemoglobin decrease', PTs from the overall AE list were included in this grouping if they appeared in the SMQs of 'haematopoietic erythropenia' and 'haematopoietic cytopenias affecting more than one type of blood cell'. PTs included in this grouping were anaemia, anaemia haemolytic autoimmune, anaemia megaloblastic, erythropenia, haematocrit decreased, haemoglobin decreased, haemolytic anaemia, iron deficiency anaemia, pancytopenia, and red blood cell count decreased. For the grouping of 'oedema', PTs from the overall AE list were included in this grouping if they appeared in the SMQ of 'haemodynamic oedema, effusions and fluid overload'. PTs included in this grouping were eye oedema, eyelid oedema, face oedema, fluid overload, fluid retention, generalised oedema, localised oedema, oedema, oedema peripheral, orbital oedema, periorbital oedema, swelling face, ascites, hypervolaemia, hydrothorax, lymphoedema, and pelvic fluid collection. For the grouping of 'hypotension', no SMQ for hypotension was available in MedDRA version 14.0 according to the sponsor. PTs included in this grouping were BP systolic decreased, hypotension, and orthostatic hypotension.

thereafter, and at the EOT/event visit. A standard 12-lead ECG was performed at screening, Month 6, and EOT/event visit.

Pivotal studies that assessed safety as a primary outcome

Not applicable.

Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies provided safety data, as follows:

- Study AC-055-201 provided data on AEs events, vital signs, body weight and physical examination findings reported as AEs, routine laboratory evaluations, and 12-lead ECG assessments.

  The study design included three consecutive periods: a single-blind placebo run-in wash-out period of two to four weeks (Period I), a double-blind treatment period of eight weeks (Period II), and a 28-day safety follow-up period starting after study drug discontinuation. In this study, treatment-emergent AEs (TEAEs) were defined as an event whose starting date was during Period II and up to 14 days after last dose (that is, up to two weeks after study drug discontinuation). Treatment-emergent serious AEs (TESAEs) were defined as an event whose starting date was during Period II and up to four weeks after study drug discontinuation. Any worsening, increased intensity or seriousness of an AE which started during Period I, was considered as a new TEAE in Period II.

  AEs occurring in Period I (defined as those with onset occurring before the day of study treatment start of Period II) were analysed in an additional safety set defined in a protocol amendment to include subjects who were not randomised. Safety results occurring in Period I were presented in the CSR and were evaluated for this report, and no safety concerns were triggered. In view of this and that this non-pivotal dose-finding study was conducted in a study population with essential hypertension, for which the sponsor was not seeking approval in this submission, and of which safety results were considered supportive, this evaluation report will summarise only treatment emergent safety events for this study (that is, safety events for the double-blind period II).

- Study AC-055B201 (MUSIC) provided data on AEs, vital signs, body weight and physical examination findings reported as AEs, routine laboratory evaluations, and 12-lead ECG assessments.

  As per instructions in the TGA's 'statement of requirements', Study AC-055B201 will be evaluated for safety only. The study design has not been previously described. This will be summarised here.

  Study AC-055B201 was a multi-centre (48 centres in 12 countries) double-blind, randomised, placebo-controlled, parallel-group, Phase II study to evaluate the efficacy, safety, and tolerability of macitentan in subjects with idiopathic pulmonary fibrosis (IPF). The primary objective was to demonstrate that macitentan positively affects the forced vital capacity (FVC) compared with placebo in subjects with IPF. Secondary objectives were to evaluate the effect of macitentan on the time to disease worsening or death in subjects with IPF and to evaluate the safety and tolerability of macitentan in this patient population. The study included a screening period of up to 28 days followed by a double-blind treatment phase that was further divided into two periods: Period 1 (fixed duration) was from randomisation up to the primary endpoint evaluation (Month 12, or earlier in case of premature discontinuation of study drug); Period 2 (variable duration) was from the primary endpoint evaluation visit up to the EOS. EOS was to be declared by the sponsor once the last randomised subject had

successfully completed Period 1 (that is, did not prematurely discontinue treatment). Prior to EOS, all subjects who had already successfully completed Period 1 were maintained on double-blind treatment during Period II until overall EOS was declared. All subjects were to have a 28-day post-treatment safety follow-up visit.

Eligible subjects were males or females aged 18 years or older at study entry, with a confirmed diagnosis of IPF within three years prior to randomisation based on the American Thoracic Society (ATS) and the European Respiratory Society (ERS) consensus criteria, and confirmed with surgical lung biopsy (SLB). Subjects were randomised in a 2:1 ratio to receive either macitentan 10 mg or matching placebo, once daily, per oral, irrespective of food intake. The primary efficacy endpoint was the change in FVC from baseline to End-of-Period 1 (EOP1). The secondary efficacy endpoint was the time to occurrence of disease worsening or death (all causes) up to EOS. A total of 178 subjects were randomised in a 2:1 ratio to the macitentan (n = 119) and placebo groups (n = 59). A total of 23 subjects (12.9%) discontinued the study prematurely (15.1% [18/119] in macitentan group; 8.5% [5/59] in placebo group), and hence 155 subjects (87.1%) completed the study. All 178 subjects were analysed for efficacy and safety. The baseline demographic characteristics were comparable between treatment groups. The majority of subjects in each treatment group were male (62.7% [37/59] and 70.6% [84/119] in the placebo and macitentan 10 mg groups) and Caucasian (96.6% [57/59] and 95.8% [114/119]). The mean (SD) age was 64.5 (6.32) and 65.1 (7.85) years. The median age was 64.0 and 66.0 years. Baseline BMI were also similar between treatment groups (mean [SD] BMI of 30.7 [5.23] and 30.5 [4.36]).

Pivotal studies that assessed safety as a primary outcome

Not applicable.

Patient exposure

In the pivotal efficacy/safety Study (AC-055-302), a total of 492 subjects received macitentan and 249 received placebo. The mean (SD) duration of treatment was 99.5 (50.82) weeks, 103.9 (52.44) weeks and 85.3 (53.65) weeks in the macitentan 3 mg, 10 mg, and the placebo groups.

The median duration of treatment was 115.6, 118.4 and 101.3 weeks. The percentage of subjects with exposure to study treatment for at least one year was 76.4%, 77.7% and 65.5%, while that for at least two years was 59.2%, 64.9% and 49.8%.

Included in Study AC-055-201 (essential hypertension study population) were a total of 252 subjects who received macitentan, 62 received placebo, and 65 received enalapril. The mean (SD) duration of treatment was 43.7 (16.8), 41.7 (17.7), 46.1 (15.3), 46.8 (16.9), 40.5 (17.8) and 44.6 (16.7) days in the macitentan 0.3 mg, 1 mg, 3 mg, 10 mg, placebo and enalapril groups.

The median duration of treatment was 50.0, 47.5, 55.0, 55.0, 45.5 and 48.0 days. The percentage of subjects with exposure to study treatment of at least 28 days was 81.0%, 72.7%, 86.9%, 82.3%, 69.4%, and 78.5%.

In Study AC-055B201 (IPF study population), a total of 119 subjects received macitentan 10 mg and 59 received placebo. The mean (SD) duration of treatment was 14.3 (4.84) and 15.4 (3.95) months in the macitentan 10 mg and the placebo groups.

The median duration of treatment was 14.5 and 15.0 months. The percentage of subjects with exposure to study treatment for at least one year was 76.5% and 81.4%.

In the 14 completed Phase I clinical pharmacology studies (AC-055-101 to AC-055-114), a total of 356 subjects (324 healthy subjects, 24 subjects with hepatic impairment, and eight subjects with severe renal impairment) were exposed to macitentan. Of the 356 subjects, 149 were exposed to single doses of macitentan and 207 received multiple doses of macitentan.

> Comments: Overall, the study drug exposure is adequate to assess the safety profile of macitentan.

Deaths and other serious adverse events

Pivotal study

The incidences of deaths were comparable between the macitentan 3 mg and the placebo groups, but lower in the macitentan 10 mg group (8.4% [21/249], 8.8% [22/250], and 6.6% [16/242] in the placebo, macitentan 3 mg, and 10 mg groups). The most commonly reported cause of death in the macitentan 3 mg group was PAH (1.2%, 2.4% and 0.8% in the placebo, macitentan 3 mg, and 10 mg groups). The most commonly reported cause of death in the macitentan 10 mg group was right ventricular failure (2.4%, 1.6% and 2.5%).

The incidences of SAEs were comparable between the macitentan 3 mg and the placebo groups, but lower in the macitentan 10 mg group (55.0% [137/249], 52.0% [130/250], and 45.0% [109/242] in the placebo, macitentan 3 mg, and 10 mg groups).

Other studies

Study AC-055-201

No deaths occurred in this study, including Periods I, II and the 28-day follow-up period. The percentages of subjects with any TESAEs were comparable among treatment groups (1.6% to 4.6%) There was no obvious trend of dose-related increased incidence of TESAEs with macitentan. No TESAE by preferred term were reported by more than one subject each.

Study AC-055B201:

The incidences of deaths were comparable between treatment groups (6.8% [4/59] and 7.6% [9/119] in the placebo and macitentan groups. The most commonly reported cause of death in the macitentan group was respiratory failure (1.7% [1/59] and 2.5% [3/119] in the placebo and macitentan groups).

The incidences of SAEs were comparable between treatment groups (33.9% [20/59] and 31.1% [37/119] in the placebo and macitentan groups). The most commonly reported SAEs in the macitentan group were worsening IPF (10.2% [6/59] and 8.4% [10/119] in the placebo and macitentan groups) and pneumonia (3.4% [2/59] and 5.0% [6/119]).

Clinical pharmacology studies:

No deaths were reported in any of the 14 clinical pharmacology studies. No SAEs were reported during macitentan treatment in these clinical pharmacology studies.

Evaluator's summary and overall conclusions on safety

Overall, safety results in the pivotal Phase III Study (AC-055-302) did not raise any major safety concerns. The incidences of all-causality AEs, treatment-related AEs, deaths, SAEs, and AEs leading to permanent discontinuation of study drug were comparable between the macitentan groups and the placebo group. The most commonly reported treatment-related AEs by preferred term in the macitentan groups were headache (2.8%, 4.0% and 5.0% in the placebo, macitentan 3 mg, and 10 mg groups), oedema peripheral (2.8%, 2.4% and 2.5%), and anaemia (0.4%, 1.6% and 3.7%).

Safety results in Studies AC-055-201 and AC-055B201 and the completed clinical pharmacology studies were generally consistent with those of the pivotal study. Safety results in Study AC-055-201 also showed that there was no obvious trend of increased incidences of TEAEs, treatment-related TEAEs, TESAEs, or TEAEs leading to study discontinuation with increasing doses of macitentan.

Known adverse drug reactions associated with ERAs include peripheral oedema, increases in liver transaminases, decreases in systemic BP and decreases in haemoglobin concentrations. Analyses of these AEs of special interest in Study AC-055-302 showed that there was no obvious increased risk of occurrence of oedema-related AEs with the macitentan groups (3 mg and 10 mg) compared to the placebo group (relative risk ratio of 0.94 for macitentan 3 mg versus placebo, and 1.03 for macitentan 10 mg versus placebo). The observed risk of occurrence of AEs associated with liver disorders and abnormal liver function was lower in the macitentan groups compared to the placebo group (relative risk ratio of 0.64 for macitentan 3 mg versus placebo, and 0.60 for macitentan 10 mg versus placebo), while that for occurrence of hypotension-related AEs was slightly higher in the macitentan groups compared to the placebo group (relative risk ratio versus placebo of 1.36 and 1.59 for macitentan 3 mg and 10 mg), and that for the occurrence of decreased haemoglobin-related AEs was 2 to 3 fold higher in the macitentan groups compared to the placebo group (relative risk ratio versus placebo of 2.32 and 3.26 for macitentan 3 mg and 10 mg).

Analyses of laboratory parameters of liver transaminases in the pivotal Study (AC-055-302) yielded results consistent with the above findings, showing that the proportion of subjects with marked elevations in ALT or AST, (defined as values > two times ULN and an increase of at least 50% from baseline) were comparable between the macitentan groups and the placebo group, as was that of subjects with ALT or AST elevations > three times ULN. Kaplan-Meier analyses showed that there was a reduced risk for occurrence of ALT or AST elevation > three times ULN with macitentan 3 mg and 10 mg compared to with placebo (hazard ratio versus placebo for the occurrence of an ALT or AST elevation > three times ULN was 0.720 and 0.635 for macitentan 3 mg and 10 mg).

Analyses of haemoglobin levels in the pivotal Study (AC-055-302) also yielded results consistent with findings of the analyses on AEs of special interest, showing that use of macitentan was associated with a decrease in haemoglobin concentration. The proportion of subjects with marked haemoglobin decreases (defined as haemoglobin < 11 g/dL and a decrease of at least 15% from baseline) was higher in the macitentan groups than in the placebo group (7.9% and 13.9% in the macitentan 3 mg and 10 mg groups versus 3.8% with placebo), as was the proportion of subjects with decreases in haemoglobin values to between > 8 g/dL and ≤ 10 g/dL at some point during the study period up to 28 days after treatment discontinuation (4.6% and 4.3% versus 3.0%), and the proportion of subjects with decreases in haemoglobin values to ≤ 8 g/dL (1.7% and 4.3% versus 0.4%). However, the proportion of subjects with these marked decreases in haemoglobin was relatively small, and this adverse drug effect is able to be monitored by routine laboratory assessments. In addition, analyses of the mean change in haemoglobin from baseline over time showed that these decreases in haemoglobin in the macitentan groups occurred within the first three months of starting study treatment, reached a minimum at around Month 3, and thereafter stabilised.

The overall estimated treatment effect over 12 months compared to placebo was small for both macitentan dose groups (–0.71 g/dL [95% CLs: –0.95, –0.48; p<0.0001] for macitentan 3 mg and –1.07 g/dL [95% CLs: –1.31, –0.84; p<0.0001] for macitentan 10 mg). Analyses of the mean change in haemoglobin from baseline over time in Studies AC-055-201 and AC-055B201 yielded similar results. Analyses in Study AC-055-201 showed a decrease in haemoglobin from baseline with macitentan until Week 8, and then with haemoglobin values returning towards baseline level and to values comparable to those of

the placebo group by Week 10. Analyses in Study AC-055B201 showed that decreases in haemoglobin in the macitentan group occurred within the first four months of starting study treatment, and thereafter stabilised.

Analyses of BP readings in the pivotal Study (AC-055-302) yielded results consistent with findings of the analyses on AEs of special interest, showing that mean changes in BP from baseline up to 28 days after treatment discontinuation were small and generally comparable across treatment groups (mean change from baseline in SBP of -1.9 and -2.4 mmHg with macitentan 3 mg and 10 mg versus -2.7 mmHg with placebo; mean change from baseline in DBP of -2.5 and -4.2 mmHg versus -2.8 mmHg). Repeated measures analysis of the change from baseline in SBP showed that the estimated treatment effect over 12 months compared to placebo was small for both dose groups and showed a relative increase rather than decrease in BP (0.16 mmHg [95% CLs: –1.62, 1.93; p=0.8637] for macitentan 3 mg, and 0.10 mmHg [95% CLs: –1.69, 1.89; p=0.9138] for macitentan 10 mg).

Analyses of the use of macitentan in subjects with hepatic impairment did not raise any increased safety concerns for macitentan in this group of patient population, but the sample size was small. Analyses of the use of macitentan in subjects with severe renal impairment also did not raise any increased safety concerns for macitentan in this group of patient population, except that there were more pronounced decreases in BP in these subjects with severe renal impairment compared to healthy subjects (median maximum decreases from baseline in SBP: -22.0 mmHg versus -3.0mmHg; DBP: -7.5 mmHg versus -3.5 mmHg). However, these changes in BP were not associated with changes in pulse rate, and were not reported as clinically relevant by the investigator, and this is an adverse effect that is monitorable by routine BP measurements. The need for monitoring of BP in patients with SRFI has been included as a precaution in the proposed PI, stating that 'Patients with severe renal impairment may experience BP reduction at treatment initiation and monitoring should be considered'.

With regards to the proposed therapeutic dose of macitentan 10 mg, safety results did not raise any particular concerns with macitentan 10 mg. Overall, the incidences of all-causality AEs, treatment-related AEs, deaths, SAEs, and AEs leading to permanent discontinuation of study drug were comparable between the macitentan dose groups. Although there was a higher risk for occurrence of hypotension-related AEs with macitentan 10 mg compared to 3 mg (relative risk ratio versus placebo of 1.36 and 1.59 for macitentan 3 mg and 10 mg), and a higher risk for the occurrence of decreased haemoglobin-related AEs with macitentan 10 mg compared to 3 mg (relative risk ratio versus placebo of 2.32 and 3.26 for macitentan 3 mg and 10 mg), evaluation of haemoglobin concentrations and BP measurements in the pivotal studies did not raise significant safety concerns, as discussed in the preceding paragraphs.

First round benefit-risk assessment

First round assessment of benefits

The benefits of macitentan in the proposed usage are:

- Treatment of PAH in terms of potential benefits in reducing morbidity/mortality and in symptom relief.

As previously discussed, the proposed therapeutic dose of 10 mg macitentan is appropriate. Hence in the discussion of the benefit-risk assessment, only reference to the macitentan 10 mg dose will be made.

Efficacy results in the pivotal Study (AC-055-302) showed that there was a statistically significant relative risk reduction of 45% (p<0.0001) with macitentan 10 mg compared to

placebo for the occurrence of a morbidity or mortality event (primary endpoint). There was also a statistically significant relative risk reduction of 50% ($p<0.0001$) with macitentan 10 mg compared to placebo for the occurrence of death due to PAH or hospitalisation for PAH.

However, further analyses suggested that these observed effects were largely due to risk reduction of morbidity rather than mortality. Competing risks analysis to explore the treatment effect on the morbidity component of the primary endpoint showed that subjects on macitentan 10 mg had a statistically significantly lower risk of disease worsening than subjects on placebo ($p<0.0001$), but no statistically significant difference was observed between the macitentan and placebo groups for the risk of death ($p=0.79$). Analyses of other death-related secondary and exploratory endpoints (time to death of all causes up to EOT, time to death of all causes up to EOS, time to death due to PAH up to EOT, and time to death due to PAH up to EOS) also suggested that macitentan does not increase survival, all yielding results showing that there was no statistically significant difference in relative risk reductions of these mortality endpoints with macitentan 10 mg compared to placebo. However, it is noted that the study was not powered for these mortality endpoints.

Analyses of the effect of macitentan on symptom relief in terms of improvements in 6MWD, WHO FC, quality of life, number of hospitalisation days per year (all-cause and PAH-related) and number of hospitalisations per year (all-cause and PAH-related) were all supportive of the beneficial effect of macitentan 10 mg on symptom relief in patients with PAH. Analyses of the effect of macitentan on exercise capacity in terms of the 6MWD showed that after six months of treatment, the placebo-corrected mean (SD) and median change from baseline in 6MWD was 22.0 m (92.58) and 15.0 m with macitentan10 mg ($p=0.0078$). A repeated measures analysis for the change in 6MWD from baseline suggested that this treatment effect of macitentan was sustained over time up to Month 12, and the estimated treatment effect over 12 months compared to placebo was 25.4 m ($p<0.0001$) with macitentan 10 mg.

Analyses of the effect of macitentan on symptom relief in terms of improvements in WHO FC from baseline to Month 6 showed that there was a 74% higher chance with macitentan10 mg compared to placebo of WHO FC improvement at Month 6 ($p=0.0063$). Analyses of the effect of macitentan 10 mg on quality of life showed that there was a statistically significant mean change from baseline (improvement) to Month 6, across all SF-36 questionnaire domains with the exception of the general health perception domain. Analyses of pharmacoeconomic endpoints showed that compared to placebo, treatment with macitentan reduced the number of hospitalisation days per year (mean all-cause hospitalisation days per year: 5.7 days with macitentan 10 mg versus 12.2 days with placebo; mean PAH-related hospitalisation days per year: 3.8 days versus 8.3 days) and the number of hospitalisations per year (mean number of all-cause hospitalisations per year: 0.5 versus 1.0 with placebo; mean number of PAH-related hospitalisations per year: 0.3 versus 0.7).

Currently-approved pharmacological treatments for PAH in Australia included ERAs (bosentan, ambrisentan), prostacyclin analogs (epoprostenol, iloprost, treprostinil), and PDE-5 inhibitors (sildenafil, tadalafil). In terms of posology and ease of administration, only ambrisentan has a comparable dosing regimen of per oral one tablet once daily. Hence, the proposed dosing regimen of macitentan of 10 mg (one tablet) once daily can offer some benefit in terms of ease of administration. A look at the effect of the currently approved ERAs (bosentan and ambrisentan) on 6MWD showed that the reported placebo-corrected treatment effects were variable, ranging from 31m to 76m. As reported in the Australian PI of bosentan, two randomised, double-blind, multicentre, placebo-controlled trials had been conducted (Studies 352 and 351), where Study 352 included 213 PAH patients, and compared two doses of bosentan (125 mg twice daily and 250 mg twice

daily) with placebo, while Study 351 included 32 PAH patients, and compared bosentan 125 mg twice daily with placebo.

Study subjects were of WHO FC III and IV at baseline, and had PAH of the following aetiology: primary pulmonary hypertension (that is, idiopathic PAH) (72%), PAH secondary to scleroderma or other connective tissue diseases (21%), or PAH secondary to autoimmune disease (7%). The mean placebo-corrected treatment effect on 6MWD for bosentan 125 mg twice daily (the recommended therapeutic dose) at four months (Study 352) was 35m, while that at three months (Study 351) was 76m. With ambrisentan, the currently-approved Australian PI reported that two randomised, double-blind, multi-centre, placebo-controlled, Phase III studies had been conducted (ARIES-1 and 2), where ARIES-1 included 201 patients and compared ambrisentan 5 mg and 10 mg once daily with placebo, and ARIES-2 included 192 patients and compared ambrisentan 2.5 mg and 5 mg once daily with placebo. Study subjects were of WHO FC II (38.4%), III (55.0%) and IV (5%) at baseline, and the majority had Idiopathic PAH (64%) and PAH associated with connective tissue disease (32%). The mean placebo-corrected treatment effect on 6MWD for ambrisentan 5 mg once daily (the recommended therapeutic dose) at Week 12 was 30.6m in ARIES-1 and 59.4m in ARIES-2.

First round assessment of risks

The risks of macitentan in the proposed usage are:

- Decrease in haemoglobin
- Hypotension

Safety analyses in the pivotal Study (AC-055-302) showed that the risk for occurrence of decreased haemoglobin-related AEs was 3.3 times higher with macitentan 10 mg compared to with placebo, and that for the occurrence of hypotension-related AEs was 1.6 times higher with macitentan 10 mg compared to with placebo.

Analyses of haemoglobin levels in the pivotal Study (AC-055-302) showed that the proportion of subjects with marked haemoglobin decreases (defined as haemoglobin < 11 g/dL and a decrease of at least 15% from baseline) was higher in the macitentan 10 mg group than in the placebo group (13.9% versus 3.8% with placebo), as was the proportion of subjects with decreases in haemoglobin values to between > 8 g/dL and ≤ 10 g/dL at some point during the study period (4.3% versus 3.0%), and the proportion of subjects with decreases in haemoglobin values to ≤ 8 g/dL (4.3% versus 0.4%). However, the proportion of subjects with these marked decreases in haemoglobin was relatively small, and this adverse drug effect is monitorable by routine laboratory assessments. In addition, analyses of the mean change in haemoglobin from baseline over time showed that these decreases in haemoglobin occurred within the first three months of starting study treatment, reached a minimum at around Month 3, and thereafter stabilised. The overall estimated treatment effect over 12 months compared to placebo was small (–1.07 g/dL [95% CLs: –1.31, –0.84; p<0.0001]). Analyses of the mean change in haemoglobin from baseline over time in Studies AC-055-201 and AC-055B201 yielded similar results.

Analyses of BP readings in the pivotal Study (AC-055-302) showed that mean changes in BP from baseline up to 28 days after treatment discontinuation were small and comparable between macitentan 10 mg and placebo (mean change from baseline in SBP of -2.4 mmHg with macitentan 10 mg versus -2.7 mmHg with placebo; mean change from baseline in DBP of -4.2 mmHg versus -2.8 mmHg). Repeated measures analysis of the change from baseline in SBP showed that the estimated treatment effect of macitentan 10 mg over 12 months compared to placebo was small and showed a relative increase rather than decrease in BP (0.10 mmHg [95% CLs: –1.69, 1.89; p=0.9138]). Safety results of Study AC-055-112, which studied the effect of macitentan 10 mg in patients with severe

renal impairment, showed that there were more pronounced decreases in BP in these subjects with severe renal impairment compared to healthy subjects (median maximum decreases from baseline in SBP: -22 mmHg versus -3.0mmHg; DBP: -7.5 mmHg versus -3.5 mmHg). However, these changes in BP were not reported as clinically relevant by the investigator, and this is an adverse effect that is monitorable by routine BP measurements.

First round assessment of benefit-risk balance

The benefit-risk balance of macitentan, given the proposed usage, is favourable.

Efficacy results showed relative risk reduction for occurrence of combined mortality or morbidity events as well as effect on symptomatic relief in terms of improvements in 6MWD, WHO FC, quality of life, number of hospitalisation days per year (all-cause and PAH-related) and number of hospitalisations per year (all-cause and PAH-related). Although analyses in the pivotal study on mortality endpoints suggested that the use of macitentan 10 mg did not improve survival, the study had not been powered for survival analyses. Safety results raised concerns only with respect to decreases in haemoglobin and to decreases in systemic BP especially in patients with severe renal impairment. However, the decreases in haemoglobin appeared to occur in the first three months of administration and thereafter stabilised. It is also an adverse effect that can be monitored by routine laboratory assessments. With macitentan 10 mg, there were more pronounced decreases in BP in subjects with severe renal impairment compared to healthy subjects, but this is an adverse effect that is monitorable by routine BP measurements.

The proposed indication for macitentan, as stated in the proposed PI, is 'for the long-term treatment of PAH in patients of WHO FC II to IV to reduce morbidity and mortality. Opsumit is effective when used as monotherapy or in combination with PDE-5 inhibitors or inhaled prostanoids'. The proposed indication for use in PAH patients of WHO FC ranging from II to IV is appropriate. Although the majority of subjects in the pivotal study were of WHO FC II (52.4%) and III (45.6%), with only 1.9% (14/739) in WHO FC IV, this reflects the composition of the target patient population in clinical practice. Subgroup analyses of the efficacy and safety endpoints in this small group of patients with baseline WHO FC IV would not have been viable in view of the very small sample size. The sponsor had performed subgroup analyses based on subgroups of baseline WHO FC I or II versus III or IV, and efficacy and safety results were generally consistent with that of the overall study population.

With regards to use of macitentan alone or as add-on therapy to PDE-5 inhibitors and prostanoids, the efficacy and safety results of the pivotal study showed that results in the subgroup of subjects with or without concomitant PAH therapy were consistent with those of the overall population. In this study 64% of subjects had concomitant PAH therapy at baseline, the majority of which were PDE-5 inhibitors (taken by 61.3% of overall study subjects [sildenafil 57.6%, tadalafil 0.9%, vardenafil 2.8%]), and the remaining were prostanoids (taken by 5.6% of overall study subjects [iloprost 3.5%, beraprost 2.0%, treprostinil 0.1%][14]). Subgroup analyses of the primary efficacy endpoint showed a consistent treatment effect versus placebo across both subgroups (with and without concomitant PAH therapy at baseline) with the 10 mg macitentan dose (hazard ratios versus placebo of 0.547 [97.5% CLs 0.392, 0.762], 0.62 [95% CLs: 0.43, 0.89] and 0.45 [95% CLs: 0.28, 0.72] in the overall study population, and in subgroups with and without concomitant PAH therapy at baseline). Subgroup analysis of safety results by concomitant PAH therapy at baseline (yes versus no) yielded results consistent with that of the overall study population.

[14] Beraprost is not currently approved for use in Australia. Vardenafil is marketed in Australia, but is not currently approved for the indication of treatment of PAH.

With regards to use in paediatric population, the sample size of adolescent subjects (12 to < 18 years old) in the pivotal study was very small (N=20). Subgroup analyses by age group of the primary efficacy endpoint and of safety data yielded results which were generally consistent with those in the overall study population, although the small sample size makes robust conclusions on the efficacy and safety of macitentan in this group of adolescent subjects difficult. A look through the currently-approved pharmacological treatments for PAH in Australia showed that only bosentan and treprostinil (restricted to age ≥ 16 years) are approved for use in paediatric patients, with a per oral twice daily maintenance dosing regimen for bosentan, and SC infusion posology for treprostinil. The evaluator does not have the information for the basis of approval in paediatric population for bosentan, but the Australian PI for bosentan stated that one open-label non-controlled study has been conducted in 19 paediatric patients with PAH. Given that no major safety issues have been observed in the paediatric subjects in the pivotal study for macitentan, it is considered that the use of macitentan in paediatric PAH patients aged 12 and above can be approved, but that the limited experience in paediatric patients should be clearly stated in the PI. In addition, it is noted that the lower limit of the weight range of subjects in the pivotal study was 36.8kg. Hence, it is recommended that a criterion of body weight ≥ 40kg be stated in the PI in addition to the age criterion of ≥ 12 years.

First round recommendation regarding authorisation

It is recommended that the application for the registration of macitentan for the long-term treatment of PAH in patients of WHO FC II to IV be approved. This is subject to a satisfactory response from the sponsor in reply to the TGA's request for further information.

Clinical questions

Efficacy

1. Please clarify regarding the information presented in Table 7 on page 83 of the CSR for Study AC-055-302 being inconsistent with the description of the statistical methods given in Section 9.7.2 of the CSR.

Rationale for question:

In describing the statistical methods for Study AC-055-302, the sponsor had presented a table in which the information presented is inconsistent with the description of the statistical methods. The source of this table was traced, leading the evaluator to a table in the Statistical Analysis Plan (SAP) which is different from the table presented in the body of the CSR but consistent with the statistical methods described in the body of the CSR. (This table is presented as Table 29 of Attachment 2). The evaluator assumed that there was a typographical error in the table on page 83 of the body of the CSR, but this needs to be clarified with the sponsor.

2. Please provide a breakdown of the relative proportion of subjects who had provided primary efficacy endpoint data at the Week 2, Week 4 and Week 8 time-points in Study AC-055-201, as well as an explanation of how the four, eight and 10-week cohorts were defined in this study.

Rationale for question:

It was noted that due to the early termination of Study AC-055-201, only approximately half of the randomised subjects (54.4%; 206/379) completed the eight week randomised treatment. In analysing the primary efficacy endpoint, in the case of a missing value at Week 8, the last available value assessed ≥ Week 2 of Period II, was carried forward.

Analyses of the primary efficacy endpoint showed that there was statistically significantly greater reduction in trough SiDBP from baseline to Week 8 compared to placebo for the macitentan 10 mg group (mean change from baseline of -11.8 mmHg versus -7.9 mmHg, p=0.0089). However, due to the early termination and the imputation method, this result was in effect an assessment of reduction in trough SiDBP from baseline to a post-baseline time-point that ranged from Week 2 to Week 8. The sponsor did not provide a breakdown of the relative proportions of subjects who had provided this data at the Week 2, Week 4 and Week 8 time-points.

It was noted that exploratory analyses of the absolute change from baseline in SiDBP for the four; eight and 10-week cohorts were performed, and results showed that the treatment effect of macitentan on the primary endpoint was reached at four weeks and then sustained until Week 8. However, the sponsor did not provide an explanation of how the four, eight and 10-week cohorts were defined in the statistical methods section of the CSR.

Safety

1. Please provide references to support the clinical relevance threshold of 30% reduction in sperm concentration indicated in Study AC-055-113

Rationale for question:

In Study AC-055-113, analysis of the change in sperm concentration from baseline to Week 12 between subjects who received only macitentan (10 mg once daily; n=14) and those who received only placebo (n=11) during the 12-week treatment period, yielded a geometric mean ratio (macitentan versus placebo) of 0.724 (90% CI: 0.47, 1.12; p=0.2173), corresponding to a 28% mean reduction in sperm concentration with macitentan. According to the sponsor, the acceptable mean reduction range for no clinically relevant treatment effect was 30%. However, the sponsor had not indicated any references to support the clinical relevance threshold of 30% reduction in sperm concentration.

Second round evaluation of clinical data submitted in response to questions

Overall, the sponsor has adequately addressed all the questions posed in the first round of evaluation. In this section on the evaluation of the sponsor's responses to the questions posed in the first round of evaluation, each question will be re-stated for ease of reference, followed by the evaluation.

Efficacy Question 1:

Please clarify regarding the information presented in Table 7 on page 83 of the CSR for Study AC-055-302 being inconsistent with the description of the statistical methods given in Section 9.7.2 of the CSR.

The sponsor confirmed that there was a typographical error in the above-mentioned table, and that the two-sided nominal type-I error level used for each comparison of active dose versus placebo to keep the study-wise type-I error to a two-sided 0.01 'conclusive' level of statistical testing was erroneously indicated as 0.025, when it should have been 0.005 as pre-specified in the Statistical Analysis Plan. The sponsor had issued an Addendum to the AC-055-302 CSR to correct this discrepancy.

As the first round of evaluation was based on the assumption that there was a typographical error in the above-mentioned table, the sponsor's response to this question has not resulted in any changes to the conclusions of the first round of evaluation.

Efficacy Question 2:

Please provide a breakdown of the relative proportions of subjects who had provided primary efficacy endpoint data at the Week 2, Week 4 and Week 8 time-points in Study AC-055-201, as well as an explanation of how the four, eight and 10-week cohorts were defined in this study.

The sponsor provided a breakdown of the relative proportions of subjects who had provided primary efficacy endpoint data at the Week 2 (Visit 4), Week 4 (Visit 5) and Week 8 (Visit 6) time-points in Study AC-055-201, showing that overall, Visit 6 measurements for the primary endpoint analysis were used for 75.4% of the patients (75.9%, 79.6%, 66.7%, 78.9%, 78.6% and 73.2% in the placebo, macitentan 0.3 mg, 1 mg, 3 mg, and 10 mg, and enalapril 20 mg groups), while Visit 4 and Visit 5 measurements were used for 9.8% and 14.5% of the patients.

The sponsor also provided explanation that for the cohort analyses, each cohort consisted of patients for whom the values at all time-points in the relevant time window (four, eight and 10 weeks) could be derived by means of a first degree Lagrange interpolation. The interpolated endpoint value was to be on treatment period and up to 28 days after the end of the study treatment. Patients with their last assessment before the relevant time-point but within an acceptability window of ± one week were assigned to the cohort, after applying a carry-forward in order to have values up to the exact scheduled time-point.

Safety Question 1:

Please provide references to support the clinical relevance threshold of 30% reduction in sperm concentration indicated in Study AC-055-113.

In its response, the sponsor acknowledged that although sperm concentration, morphology, and motility are useful tools to evaluate infertility, the correlation between values outside the (wide) normal range and fertility is not strong. According to the sponsor, the selection of the 30% threshold was based on a study performed by Amory et al. [15], in which the effect of dutasteride and finasteride on semen parameters and serum hormones in healthy men was evaluated In this study a clinically significant difference of 30% in sperm concentration was used, which was derived from human studies of male fertility and effectiveness of hormonal contraceptives, using impairment of fertility as standard. The sponsor provided further support for the selection of the 30% threshold, stating that the same threshold had been used in a clinical study in which the possible effects of bosentan on testicular function were studied in patients with PAH (Clinical Study Report AC-052-402, Submission No. PM-2010-01202-3-3, May 2010).

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of macitentan in the proposed usage are unchanged from those previously identified.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of macitentan in the proposed usage are unchanged from those previously identified.

[15] Amory JK et al., 2007. The effect of 5alpha-reductase inhibition with dutasteride and finasteride on semen parameters and serum hormones in healthy men. J Clin Endocrinol Metab, 92:1659-65.

Second round assessment of benefit-risk balance

The benefit-risk balance of macitentan, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

It is recommended that the application for the registration of macitentan for the long-term treatment of PAH in patients of WHO FC II to IV be approved.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU Risk Management Plan (EU-RMP) Version 1 (dated 05/10/2012, DLP 26/04/2012) with Australian Specific Annex (ASA) Version 1.0 (18/01/2013) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the non-clinical aspects of the Safety Specification (SS) by the Toxicology area of the OSE and the clinical aspects of the SS by the OMA, the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows (Table 7):

Table 7: Important identified and potential risks and missing information

Risks/Concerns	
Important identified risks	Anaemia, decrease in haemoglobin concentration
Important potential risks	Teratogenicity Hepatotoxicity Hypotension Thrombocytopenia Leukopenia Menstrual disorders Ovarian cysts
Other safety concerns	Off-label use, for example in paediatric patients
Missing information	Paediatric PAH patients below 12 years of age PAH patients with moderate to severe hepatic impairment PAH patients with severe renal impairment and/or undergoing dialysis

OPR reviewer comment:

Notwithstanding the evaluation of the non-clinical and clinical aspects of the SS, some additional ongoing safety concerns should be considered.

Ongoing safety concerns

The sponsor should add the following as Ongoing Safety Concerns:

Important potential risks:

- Vasculitis;
- Reduction in male fertility; and
- Peripheral oedema/veno-occlusive disease.

Important missing information:

- PAH patients with HIV infection; and
- PAH patients with chronic haemolytic anaemia.

Male fertility

It is noted the sponsor had conducted a trial in healthy volunteers to assess male fertility. It is requested the sponsor submit details of the study (including, but not limited to study design, results and interpretation of the results) to assess whether reduction in male fertility should be an Ongoing Safety Concern.

Pharmacovigilance plan

The sponsor proposes only routine pharmacovigilance activities for important identified and potential risks and missing information (as stated above).

The sponsor is not proposing any additional studies to evaluate the Ongoing Safety Concerns further.

It is suggested the sponsor conduct relevant and appropriate additional pharmacovigilance activities to address the following Ongoing Safety Concerns:

- Hepatotoxicity (due to inconclusive data from trials);
- Thrombocytopoenia/Leukopaenia (due to insufficient data presented);
- PAH patients with moderate to severe hepatic impairment;
- PAH patients with severe renal impairment;
- PAH patients with HIV infection; and
- PAH patients with chronic haemolytic anaemia.

Sponsor's conclusion in regard to the need for risk minimisation activities

The sponsor states that additional risk minimisation activities were necessary for the following Ongoing Safety Concerns:

- Anaemia;
- Hepatotoxicity;

- Teratogenicity; and
- Off-label use.

The sponsor states that for the remaining Ongoing Safety Concerns, routine risk minimisation activities are sufficient.

OPR reviewer comment:

The sponsor's conclusion is acceptable.

Potential for medication errors:

For the purposes of this RMP evaluation different types of medication errors, as suggested by Ferner & Aronson (2006)[16], have been considered.

OPR reviewer comment:

The sponsor's actions regarding name confusion, labelling and presentation are considered acceptable.

Potential for overdose

The risk for overdose is low. In the proposed PI, overdosage and its management have been discussed to a satisfactory standard.

Potential for off-label use

Macitentan could potentially be used to manage IPF. At this stage the use for IPF would be off-label.

The proposed indication is adequately described in the proposed PI, and this drug will be almost exclusively prescribed by PAH specialists, but there is a potential for off-label use.

Potential for paediatric off-label use

The sponsor recognises that macitentan is only indicated for adults and children over the age of 12 years. This is reflected in the proposed PI. This is considered acceptable.

Risk minimisation plan

Planned actions

Additional risk minimisation activities are proposed for macitentan.

The sponsor is planning the following additional risk minimisation activities (see Table 8):

- Prescribing checklist;
- HCP Brochure; and
- Patient card.

Furthermore, in Australia, macitentan will be classified as a Schedule 100 drug, that is, prescription by PAH specialists only.

[16] Ferner RE, Aronson JK 2006. Clarification of terminology in medication errors: definitions and classification. Drug Saf 29:1011–1022.

It is noted that the sponsor is planning to evaluate the effectiveness of the additional risk minimisation activities pre- and post-launch.

OPR reviewer comment:

The additional risk minimisation activities outlined by the sponsor seem reasonable and appropriate, except for some issues outlined below.

The sponsor is advised to submit the details of the Australian versions of the Prescribing checklist, the HCP Brochure; and Patient card.

The sponsor should make the results of the additional risk minimisation activity evaluations (pre- and post-launch) available within the submitted PSURs.

In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft PI document be revised as follows:

> In the 'Precautions' section, the PI should include a statement that macitentan discontinuation should be considered in treatment-related pulmonary veno-occlusive disease (or a statement to that effect).
>
> In the 'Adverse Events' section, the PI should list values for haemoglobin in the more commonly used unit g/L rather than g/dL.
>
> In the 'Overdosage' section, the PI should contain the Poisons Information contact telephone number.

In regard to the proposed routine risk minimisation activities, the draft consumer medicine information (CMI) document is considered satisfactory.

In regard to the proposed additional risk minimisation activities, it is recommended to the sponsor to undertake the following:

> On the 'Opsumit Prescriber Checklist', the liver function test results should include fields for albumin, ALP, and GGT, to accommodate that intrinsic liver damage may not be shown by abnormal ALT or AST only.
>
> Establish a patient registry similar to the register for Tracleer (bosentan).

Table 8: Additional risk minimisation activities planned by the sponsor regarding certain safety concerns

Activity	Aims
Prescribing checklist	To ensure appropriate usage of Opsumit by reminding HCP of the contra-indications, warnings and precautions, and of the need to provide patients with appropriate information regarding the product. To remind HCP to dispense the patient card.
HCP Brochure	To educate prescribers and other HCPs on key safety information related to Opsumit (contraindications, warnings, supportive information regarding contraception), on the need to have appropriate communication with the patient prior to initiation of and during treatment, and about the need to report pregnancies using pregnancy AE forms. To inform prescribers and other HCPs about symptoms of potential adverse drug reactions (ADRs) and on the need to report them.

Activity	Aims
Patient card	To educate patients about the potential risk of teratogenicity associated with Opsumit treatment. To inform patients where to obtain more information about their treatment. To educate patients on the need to report immediately to their prescribing physician any pregnancy that may occur, as well as symptoms and signs of any potential ADR.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP (EU Risk Management Plan (EU-RMP) U12-1933-01 Version 1.0 (dated 26/07/2012, DLP 21/03/2012) with Australian Specific Annex (ASA) Version 1.0 (dated 10/09/2012)) is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; the submitted EU-RMP is applicable without modification in Australia unless so qualified; and the draft PI and CMI documents should NOT be revised until the Delegates Overview has been received:

Further safety considerations

1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated request for further information and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.

Unless the sponsor can provide compelling justification against any of the following recommendations, the following should be considered:

Recommendations in regard to ongoing safety concerns

2. The sponsor should add the following as Ongoing Safety Concerns:
    a. Important Potential Risks:
        - Vasculitis;
        - Reduction in male fertility; and
        - Peripheral oedema/veno-occlusive disease.
    b. Important Missing Information:
        - PAH patients with HIV infection; and
        - PAH patients with chronic haemolytic anaemia.
3. It is noted the sponsor had conducted a trial in healthy volunteers to assess male fertility. It is requested the sponsor submit details of the study (including, but not limited to study design, results and interpretation of the results) to assess whether reduction in male fertility should be an Ongoing Safety Concern.

Recommendations in regard to pharmacovigilance activities

4. It is suggested the sponsor conduct relevant and appropriate additional pharmacovigilance activities to address the following Ongoing Safety Concerns:
   - Hepatotoxicity;
   - Thrombocytopaenia/Leukopaenia;
   - PAH patients with moderate to severe hepatic impairment;
   - PAH patients with severe renal impairment;
   - PAH patients with HIV infection; and
   - PAH patients with chronic haemolytic anaemia.

Recommendations in regard to risk minimisation activities

5. The sponsor is advised to submit the details of the Australian versions of the Prescribing checklist, the HCP Brochure; and Patient card.
6. The sponsor should make the results of the additional risk minimisation activity evaluations (pre- and post-launch) available within the submitted PSURs.
7. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft PI document be revised as follows:
   a. In the 'Precautions' section, the PI should include a statement that macitentan discontinuation should be considered in treatment-related pulmonary veno-occlusive disease (or a statement to that effect).
   b. In the 'Adverse Events' section, the PI should list values for haemoglobin in the more commonly used unit g/L rather than g/dL.
   c. In the 'Overdosage' section, the PI should contain the Poisons Information contact telephone number.
8. In regard to the proposed additional risk minimisation activities, it is recommended to the sponsor to undertake the following:
   a. On the 'Opsumit Prescriber Checklist', the liver function test results should include fields for albumin, ALP, and GGT, to accommodate that intrinsic liver damage may not be shown by abnormal ALT or AST only.
   b. Establish a patient registry similar to the register for Tracleer (bosentan).

Second round risk management plan advice

Table 9 seeks to reconcile issues identified in the RMP evaluation report for the above submission with consideration of the following documents:

1. EU Risk Management Plan (EU-RMP) Version 3 (dated 12/08/2013, DLP 26/04/2012 with Australian Specific Annes (ASA) Version 1.0 (dated 22/08/2013).
2. Sponsor's response to the TGA request for further information, dated 21 August 2013.
3. OMA Clinical Evaluation Report (first round dated 19 June 2013; second round dated 27 September 2013.
4. OSE, Non-clinical Evaluation Report (NCER), (dated 20 September 2013).

It is considered that the sponsor's response to the TGA request for further information has adequately addressed some of the issues identified in the RMP evaluation report. The outstanding issues are specified in Table 9. Additional recommendations have been made.

Table 9: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.	'Point acknowledged. Nonclinical and Clinical Evaluation Reports have not been received at the time of writing this S31 response.'	This is considered acceptable.
The sponsor should add the following as Ongoing Safety Concerns: Important Potential Risks: Vasculitis;	In the current European RMP for Tracleer (bosentan), vasculitis is no longer included as an Important Potential Risk. Close monitoring of all reported vasculitis cases was performed during the 11 years' post-marketing period of Tracleer. In the latest (18th) PSUR/PBRER covering the period up to 19 November 2012, the sponsor provided a cumulative review of cases of vasculitis: In 20 placebo-controlled bosentan studies across all indications, and including 1,838 placebo- and 2,486 bosentan-treated patients at doses up to 2,000 mg/day, the incidence of vasculitis using 'Vasculitis' SMQ was identical in placebo and bosentan groups (0.3 %). Based on analysis of a cumulative number of 52 post-marketing reports of	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
	vasculitis received since Tracleer IBD, underlying autoimmune CTDs and concomitant medications were strong confounding factors in reported cases. There is no clear evidence of a causal relationship between vasculitis and bosentan administration. In the final PRAC PSUR assessment report, dated 13 June 2013, the EU assessor commented: *"Regarding the review of vasculitis, the assessor agrees with the MAH that there is no clear evidence of a causal relationship between the event and bosentan when the presence of underlying autoimmune collagen vascular diseases in this PAH patient population is taken into consideration, and given the fact that most patients also received multiple concomitant medications. However, as proposed by the MAH this issue should continue to be closely monitored".* Based on the cumulative review of vasculitis and in line with the *Guidance on format of the risk management plan (RMP)* in the EU and the *Guideline on good pharmacovigilance practices Module VII: Periodic Safety Update Report*, vasculitis has been categorised as other potential risk, not important, and removed from the Tracleer EU RMP. Based on these considerations and the available clinical data with macitentan presented in the previous response, the Applicant recommends not to include vasculitis as an Important Potential Risk in the AU RMP for macitentan. Any case reports of vasculitis will be closely monitored and analysis of aggregated data will be presented in PSURs/PBRERs.	
Reduction in male fertility; and	'Based on the above, patients treated with macitentan do not seem to be at increased risk of developing testicular disorders and/or infertility; nevertheless, in line with the EU RMP,	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
	testicular tubular atrophy (testicular disorders and/or infertility) will be included as an Important Potential Risk in the RMP. Individual case reports of testicular disorders or infertility will be closely monitored and data analysis will be presented in the PSUR.'	
Peripheral oedema/veno-occlusive disease.	'Therefore, considering the very similar or even lower incidence rates of oedema AEs in the macitentan treatment groups compared to placebo, especially when adjusted for patient-years of exposure, the Applicant proposes not to include peripheral oedema as an Important Potential Risk in the RMP, as is also consistent with the EU RMP; however, individual case reports of peripheral oedema will be closely monitored and aggregated data will be presented in the PSUR as part of routine pharmacovigilance activities.'	This is considered acceptable.
Important Missing Information: PAH patients with HIV infection; and	The sponsor agrees to the addition of PAH patients with HIV infection as important missing information within the OPSUMIT RMP Australian Specific Annex. The updated Annex will be provided in a subsequent submission.	The sponsor has agreed to include PAH patients with HIV infection. This is considered acceptable.
PAH patients with chronic haemolytic anaemia.	'Ongoing safety concerns within the EU RMP include 'Anaemia, decrease in haemoglobin concentration' as an Important Identified Risk. As described in Annex 12, Section 1.1 of V 3.0 of the EU RMP, the MedDRA Preferred Terms 'Chronic Anaemia' and 'Haemolytic Anaemia' are included in the subgroup "Anaemia", and are therefore already identified as Important Identified Risks. The Applicant therefore does not agree to specifically include 'PAH patients with chronic haemolytic anaemia' under Important Missing Information in the Ongoing Safety Concerns. Individual case reports of anaemia (including chronic haemolytic anaemia) will be closely monitored and data analysis will	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
	be presented in PSURs as part of routine pharmacovigilance activities.'	
It is noted the sponsor had conducted a trial in healthy volunteers to assess male fertility. It is requested the sponsor submit details of the study (including, but not limited to study design, results and interpretation of the results) to assess whether reduction in male fertility should be an Ongoing Safety Concern.	'Study AC-055-113, entitled "A single-center, double-blind, randomized, placebo-controlled, parallel-group study to investigate the effects of a 12-week once daily treatment with macitentan 10 mg on spermatogenesis in healthy male subjects", was submitted as part of the MAA and is located in Module 5.3.4.1, volumes 28–33.'	This is considered acceptable.
It is suggested the sponsor conduct relevant and appropriate additional pharmacovigilance activities to address the following Ongoing Safety Concerns: Hepatotoxicity;	To further confirm and characterise the hepatic safety profile of Opsumit (macitentan) based on post-marketing experience, the sponsor has already initiated the following routine and additional Pharmacovigilance activities on a global basis: Routine Pharmacovigilance activities: The sponsor will conduct detailed follow-up of all events suggestive of potential drug induced liver injury (with or without associated clinical symptoms). These reports will be processed as high priority cases. The Drug Safety Physician will intensively monitor all reports (irrespective of seriousness or causality, from worldwide post-marketing or clinical trials sources). Targeted hepatic AE questionnaire: All events suggestive of drug induced liver injury will receive prompt internal medical review, and extensive focused follow-up activities, using a targeted hepatic AE questionnaire designed to collect detailed information regarding clinical description, risk factors, diagnostic evaluation, management, and. If no response is received, repeated follow-up attempts will be made as per	The sponsor is already conducting 'A long-term prospective observational study (product exposure registry) to evaluate potential serious hepatic risks related to the use of Opsumit (macitentan)' and an assessment and analysis of reports of serious hepatic adverse events in the US. The sponsor should assign these activities to the 'hepatotoxicity' ongoing safety concern.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
	Actelion follow-up procedure for high priority case. Thorough analysis and assessment of all hepatic safety data including reported Hepatic Adverse Events of Special Interest (HAESI) 1 from all global sources will be provided in the PSURs / Periodic Benefit Risk Evaluation Reports (PBRERs). The analysis will include evaluation of the frequency, nature, severity, risk factors, alternative causes, clinical management, and outcomes of any potential drug induced liver injury, and will also include further analysis on PAH patients treated with macitentan with a medical history of moderate to severe hepatic impairment. Additional Pharmacovigilance activities: An Independent Liver Safety Board (ILSB) has been established to provide review and assessment of each individual case report containing HAESI reported from all global sources as agreed upon and defined in the ILSB charter. The ILSB will also perform ad-hoc review of emerging data that require specific attention (e.g. increased frequency or unusual pattern of specific hepatic AE(s), published case report or case series, etc). The ILSB will also review the hepatic safety data analysis that will be provided in PSURs / PBRERs. Additional safety data from all ongoing and planned clinical studies with macitentan in PAH and other indications will provide a valuable source of information. Analysis of integrated data regarding liver function test values and hepatobiliary / investigation adverse events from these clinical studies will be performed as documented in the current proposed RMP.'	
PAH patients with HIV infection; and	To closely monitor and further characterise the risk and assess any causal relationship, the sponsor proposes the following routine and	Routine pharmacovigilance may be sufficient.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
	additional Pharmacovigilance activities: Routine Pharmacovigilance activities: The sponsor will conduct extensive follow-up of all events reported in macitentan treated patients with HIV. These reports will be processed as high priority cases. The Drug Safety Physician will intensively monitor all reports (irrespective of seriousness or causality, from worldwide post-marketing or clinical trial sources). In order to collect additional information, DCFs will be sent to the reporter as appropriate. Extensive and repeated follow-up attempts will be made as per Actelion follow-up procedure for high priority cases. The sponsor will analyse all macitentan cases with events reported in patients with HIV and will provide thorough aggregated data analysis in the PSURs/PBRERs. These will also include further detailed analysis for patients with concomitant lopinavir+ritonavir or other ritonavir-boosted protease inhibitor treatment, to identify any unusual pattern of AEs or evidence suggesting DDI. Additional Pharmacovigilance activities: Additional safety data from all ongoing and planned clinical studies with macitentan will provide a valuable source of information. Integrated safety data analysis regarding patients with HIV from these clinical studies will be performed.	
The sponsor is advised to submit the details of the Australian versions of the Prescribing checklist, the HCP Brochure; and Patient card.	'The Applicant would like to submit the Australian version of the Prescribing Checklist, the HCP Brochure, and Patient Card at a later stage of the evaluation, following receipt of the clinical evaluation report and when there is greater clarity surrounding the AU PI content.'	This is considered acceptable.
The sponsor should make the results of the	'The results of the risk minimisation actions described in the EU RMP, ASA	This is considered

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
additional risk minimisation activity evaluations (pre- and post-launch) available within the submitted PSURs.	and within these responses will be described in PSURs.'	acceptable.
In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft PI document be revised.	Appropriate changes have been made by the sponsor.	This is considered acceptable.
In regard to the proposed additional risk minimisation activities, it is recommended to the sponsor to undertake the following: On the 'Opsumit Prescriber Checklist', the liver function test results should include fields for albumin, ALP, and GGT, to accommodate that intrinsic liver damage may not be shown by abnormal ALT or AST only.	The sponsor agrees to add the proposed laboratory variables to the prescriber checklist for patients in Australia.	The sponsor agreed to make the necessary changes on the checklist. This is considered acceptable.
Establish a patient registry similar to the register for Tracleer (bosentan).	The Bosentan Patient Registry (BPR) was set up in Australia as part of a risk-sharing agreement between the Sponsor and the Australian Pharmaceutical Benefits Advisory Committee (PBAC) to allow setting a price and obtaining reimbursement. The BPR objectives did not include objectives related to the Tracleer (bosentan) safety profile. The BPR was completed five years ago, and published in 2011 [Keogh 2011[17]]	If the sponsor agrees to include the additional pharmacovigilance activities conducted in the US, another registry is not absolutely necessary, but considering that the sponsor has a

[17] Keogh A, et al. 2011. The bosentan patient registry: long-term survival in pulmonary arterial hypertension. Int Med J; 41:227-234.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
	Given that Opsumit will be a Section 100 medication in Australia, to be prescribed only from Medicare-approved 'Designated Centres', Opsumit will be prescribed by PAH specialists who will be fully familiar with the risks of other ERAs, and having the necessary facilities to oversee close monitoring of patients. Physicians within the Designated Centres are responsible for ensuring that all patients prescribed Opsumit undergo the necessary monitoring tests. The Sponsor will ensure that prescribers in all Designated Centres will be educated on the specific safety concerns and appropriate use and monitoring necessary when prescribing Opsumit. In this setting, the characterisation of the post-marketing safety profile of Opsumit is best served by careful routine and additional pharmacovigilance activities. The sponsor is of the opinion that these measures are sufficient to further define the Opsumit safety profile. In conclusion, the sponsor is of the opinion that an additional registry to characterise the Opsumit safety profile is not needed. Of note, no such registry was required for Volibris (ambrisentan) in Australia.	registry infrastructure in place for Tracleer, and could include macitentan with minimal effort, this would be considered beneficial.

VI. Overall conclusion and risk/benefit assessment

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

Quality

The quality evaluator has recommended approval for macitentan. The chemistry and quality control, product specifications, shelf life of two years, storage temperature, GMP clearances, labels and PI are acceptable. The absolute bioavailability of macitentan is not known but the sponsor had provided an acceptable justification given the poor solubility and chemical instability of the active ingredient. Using computer modelling, the estimated oral bioavailability was 74%. The PK of macitentan and its metabolite were not affected by food. The pivotal study used a tablet formulation that is the same as proposed for registration however early Phase I and II studies used a capsule formulation. A relative bioavailability study comparing the tablet with capsule showed they were bioequivalent

for AUC for the active and metabolite but slightly bioinequivalent for the active on C_{max} with the tablet being on average 18% lower than the capsule. Given the chronic dosing nature of macitentan, implying that AUC is more relevant, and that data are available using the tablet from the pivotal study then this is not likely to be clinically significant. This is consistent with the EU guideline on this matter that notes that there is no requirement to demonstrate bioequivalence between Phase II and Phase III formulations since any differences would be taken into account in the design of the Phase III studies.

Nonclinical

The nonclinical evaluator has no objections to the registration of macitentan. The dossier was comprehensive and of high quality. Macitentan and its active metabolite are competitive antagonists of ET_A and ET_B receptors and macitentan was more potent than bosentan but had similar potency to ambrisentan. It has a longer receptor occupancy half-life than both of these and was also more effective at lowering BP and inhibiting induction of pulmonary fibrosis in rat models of PAH. Safety pharmacology studies did not identify any unexpected clinical hazards. No effects on hERG-mediated K+ channels were seen at clinical plasma levels. CYP3A4 was the major metabolising enzyme along with CYP2C19 playing a minor role. Macitentan showed no significant inhibition of CYP enzymes and was neither a substrate nor inhibitor of PgP or organic anion transporting polypeptides (OATP1B1 and OATP1B3). Potential target systems for toxicity include liver (high doses), haematopoietic (anaemia), testis (four to 14 times clinical exposure) and vasculature (multicentric arteritis/periarteritis like other ERAs). There was no evidence of mutagenicity or carcinogenicity but it was teratogenic (class effect for ERAs, Category X) and fetotoxic.

Clinical

The clinical evaluator has recommended approval for macitentan with a revised indication to remove the claim for a reduction in morbidity and mortality and to add the proportion of subgroups of PAH in which efficacy was demonstrated. The evaluator commented that there is potential benefit of macitentan for the treatment of PAH in terms of reducing morbidity and mortality and in symptom relief and there are risks in terms of hypotension and decreases in haemoglobin with limited data in the paediatric population (12 to < 18 years).

The clinical dossier included the following data:

- 14 pharmacology studies
- one PopPK analysis
- one pivotal clinical study [SERAPHIN]
- two other clinical studies

Pharmacology

The pharmacology studies noted the following findings:

- Macitentan t_{max} is 8 hours, t½ is 16 hours, steady state three days and volume of distribution is 40 L.
- Macitentan is metabolised to an active metabolite via CYP3A4 and to a lesser extent by CYP2C19.
- Active metabolite t_{max} is 24 hours; t½ is 48 hours and steady state seven days.

- Food did not affect exposures for macitentan or metabolite.
- Highly protein bound and extensively metabolised with no unchanged drug recovered in urine.
- Renal excretion was the most important route of elimination
- Population modelling showed the target PAH population would have trough concentrations of macitentan at 1.6 to 2.3 times healthy controls.
- AUC and C_{max} of macitentan were decreased in healthy subjects with mild (↓21% AUC), moderate (↓34% AUC) and severe (↓6% AUC) hepatic impairment compared to controls. Active metabolite was also reduced. Safety results were acceptable. These results did not indicate a need for dose adjustment.
- AUC and C_{max} were higher in severe renal impairment by 24% and 11% respectively with the active metabolite being 58% and 39% higher. Safety results showed reductions in BP in this group. These results did not indicate a need for dose adjustment but a precaution was added regarding BP reduction and monitoring recommended.
- No clinically relevant drug interactions were observed with warfarin, sildenafil and cyclosporine. Ketoconazole led to a 2.32 fold increase in macitentan AUC and a 26% decrease in active metabolite with acceptable safety. The evaluator agreed with the sponsor that these changes were acceptable and did not require a change in macitentan dosing. Rifampicin decreased macitentan by 79% on AUC_T but not the metabolite and the evaluator agreed with the sponsor that no dose adjustment is required but a precaution has been included on potentially reduced efficacy.
- PD data indicated that 10 mg appeared to be close to the plateau of the pharmacological effect and 3 mg appeared to be the lowest dose showing relevant hemodynamic effects, thus supporting both strengths for the pivotal trial.

Efficacy

Study SERAPHIN (AC-055-302): This was a Phase III, multi-centre, multi-national, randomised, double blind, placebo controlled, parallel group study of 3 mg macitentan daily, 10 mg macitentan daily and placebo daily in 742 subjects (80% completion, 9% major protocol violations) with symptomatic PAH. Concomitant medications were allowed (64% of subjects) and included phosphodiesterase inhibitors (sildenafil 58% of subjects) and inhaled prostanoids (iloprost 3.5% of subjects) but other ERAs and IV or SC prostanoids (for example, epoprostenol, treprostinil) were not allowed. This was an event driven trial with a target of 285 events and included patients from PAH WHO Groups 1.1 to 1.3 of the Venice classification that is, idiopathic, familial, collagen vascular disease, simple congenital systemic to pulmonary shunts, HIV infection, drugs or toxins but not patients with significant venous or capillary involvement (for example, PVOD) or persistent pulmonary hypertension of the newborn. Inclusion/exclusion criteria were considered acceptable and consistent with EU guidelines. Baseline demographic characteristics were comparable between groups (77% female, mean age 46 years, n=13 aged 12 to < 18 years on macitentan) as to where haemodynamics and disease characteristics (mean PAH diagnosis time of 2.7 years, idiopathic PAH (55%), collagen vascular disease (31%), congenital shunts (8%), drugs and toxins (3%), HIV (1%), mean 6MWD of 360m, WHO FC II (52%), WHO FC III (46%), WHO FC IV (2%)).The primary efficacy endpoint, using a time to event analysis, of first morbidity or mortality event (death or AE leading to death within four weeks of study discontinuation, atrial septostomy or hospitalisation for it, lung transplantation or hospitalisation for it, initiation of IV or SC prostanoids or hospitalisation for it or worsening of PAH) occurred in:

- 38% on macitentan 3 mg (HR 0.704, 97.5%CI 0.516-0.960 p=0.0108)
- 31% on macitentan 10 mg (HR 0.547, 97.5% CI 0.392-0.762 p<0.0001)
- 46% on placebo

that is, a 30% and 45% reduction in the primary endpoint for 3 mg and 10 mg macitentan. The number needed to treat (NNT) for 10 mg macitentan was 6.1 at two years. Only the 10 mg dose was considered to be a conclusive result based on the statistical design. The Kaplan-Meier curve showed a separation by six months. The per-protocol results were consistent with the above all-randomised set population. The components of the primary endpoint showed it was predominantly driven by worsening of PAH with death showing a similar result between placebo (6.8%) and 10 mg macitentan (6.6%). Subgroup analyses were generally consistent with the overall population including those with and without other PAH treatments at the 10 mg dose (HR 0.62 with and HR 0.45 without concomitant PAH treatments), age (< 18 versus 18 to 64 versus > 64 years), baseline WHO FC (I/II versus III/IV) and aetiology of PAH (idiopathic/other versus collagen vascular disease versus congenital shunts). Secondary efficacy endpoints showed a placebo subtracted mean difference in 6MWD at six months of 16.8m on 3 mg macitentan and 22m on 10 mg macitentan. Improvement in WHO FC at six months occurred in 19.8% on 3 mg macitentan (RR 1.54, p=0.0395) and 22.3% on 10 mg macitentan (RR 1.74, p=0.0063) compared with 12.9% on placebo. Death due to PAH or hospitalisation due to PAH, showed a relative risk reduction of 33% on 3 mg macitentan and 50% on 10 mg macitentan. A non-significant 36% relative risk reduction in death from all causes was seen for 10 mg macitentan but not for 3 mg macitentan. A number of exploratory endpoints, including improvements in WHO FC, Borg dyspnoea index and quality of life (SF-36, except general health perception domain) appeared supportive.

Study AC-055-201: This was a proof of concept, dose finding study in essential hypertension that was terminated early (54% completed eight weeks) due to lack of expected benefit and a safety analysis was conducted of five patients with elevated liver enzymes on macitentan. A significant reduction in SiDBP was observed on 10 mg macitentan (-11.8 mm Hg versus -7.9 mm Hg on placebo, p=0.0089) at Week 2 to 8 depending on measurement.

Safety

The pivotal study had 492 patients exposed to macitentan with a mean 104 weeks duration on 10 mg macitentan (78% one year and 65% for two years). Any AEs were reported with similar frequencies across the three groups of placebo, 3 mg and 10 mg macitentan (about 96% of subjects) with the most common on macitentan 10 mg versus placebo being PAH (22% versus 35%), upper respiratory tract infection (15% versus 13%), peripheral oedema (18% versus 18%), nasopharyngitis (14% versus 10%), right ventricular failure (13% versus 23%), headache (14% versus 9%), anaemia (13% versus 3%), bronchitis (12% versus 6%) and dizziness (11% versus 11%). Adverse drug reactions were reported with similar frequency overall across the groups but there were some differences for 10 mg macitentan versus placebo such as headache (5% versus 2.8%), abnormal liver function test (2.1% versus 1.2%), anaemia (3.7% versus 0.4%), thrombocytopenia (2.1% versus 0.8%), hypotension (1.7% versus 0.8%). SAEs were overall comparable across groups with the most common being PAH and right ventricular failure (both less on macitentan 10 mg than placebo). Overall deaths were slightly less on 10 mg macitentan than placebo (6.6% versus 8.4%) with the most common reason being right ventricular failure. Discontinuations due to AEs were similar with most common reason being PAH and right ventricular failure.

Changes in liver function were seen on macitentan with higher rates of ALT > three times ULN at 3.4% versus 1.6% and ALT > eight times ULN at 2.1% versus 0.4%. ALT or AST >

three times ULN returned to normal at a median nine and 18 days respectively. Another study suggested a dose dependent association with elevations in ALT or AST and further study also showed increases in ALT and AST that were greater on macitentan than placebo. One subject in the hepatic impairment study with mild hepatic impairment has clinically significant increases in ALT (8.1 times ULN).

Renal function and clinical chemistry changes were low and comparable across groups. Decreases in haemoglobin were seen on macitentan 10 mg versus placebo at -11 g/L versus -1 g/L with marked decreases also greater (13.9% versus 3.8%) and marked decreases in leucocytes (5.2% versus 0%) and platelets (8.3% versus 3.4%) were also seen. Changes in vital signs were small and comparable (DBP placebo subtracted difference of -0.64mmHg). ECG abnormalities were comparable (45% versus 54%) including for QT changes and the thorough QT study was negative. A testicular safety study indicated a 28% reduction in sperm concentration. Seven pregnancies occurred in the pivotal study.

AEs of special interest with macitentan versus placebo include oedema (21% versus 20%), decreased haemoglobin (16% versus 5%), liver disorders and abnormal liver function (9% versus 15%) and hypotension (7% versus 4%). Subgroup analysis of these events was consistent with the general population. Safety in special populations showed a consistent finding by age, no trend for increasing AEs with increased severity of hepatic impairment or in severe renal impairment (except for BP reductions). Drug interaction studies showed no additional concerns but AEs were higher on the combination. Safety findings from the other studies are discussed in Attachment 2.

Risk management plan

The Office of Product Review has accepted the Macitentan EU Risk Management Plan for Opsumit (macitentan), version 3, dated 12 August 2013 (DLP 26 April 2012), with the Australian Specific Annex, version 1.0, dated 22 August 2013.

The following were outstanding matters and should be followed up with OPR and in the Pre-ACPM Response:

- Ongoing Safety Concern: Hepatotoxicity: The sponsor was requested to undertake additional pharmacovigilance activities to address this ongoing safety concern but has outlined risk minimisation activities instead. Given that the sponsor is undertaking a long term prospective observational (product exposure registry) study to evaluate potential serious hepatic risks related to the use of macitentan and an assessment and analysis of reports of serious hepatic AEs in the US, then the sponsor should assign these activities to the hepatotoxicity ongoing safety concern.
- Ongoing Safety Concerns: Thrombocytopenia, leucopoenia, moderate to severe hepatic impairment, severe renal impairment, HIV infection: The sponsor was requested to undertake additional pharmacovigilance activities to address these ongoing safety concerns but has outlined risk minimisation activities instead such as PI amendments. The response is acceptable to OPR to undertake routine pharmacovigilance along with the PI changes.
- Patient registry: The sponsor has a patient registry for bosentan to model long term survival outcomes as part of a risk sharing agreement with the Pharmaceutical Benefits Advisory Committee. Given the data in this submission, the sponsor disagreed that another registry is required. OPR recommended it should be established for macitentan and it could be used as an additional pharmacovigilance activity and risk minimisation activity. If the sponsor agrees to include the additional pharmacovigilance activities conducted in the US for hepatotoxicity, then another

registry may not be needed. The sponsor should clarify if Australian patients will have access to this registry.

- Ritonavir and lopinavir: The sponsor should clarify the rationale for why the macitentan PI says the increase in its exposure with ritonavir and lopinavir is only expected to be about two times but that the data for bosentan shows the increase in bosentan is about 48 times initially and then decreases to five times.

Delegate considerations

Efficacy: Macitentan has demonstrated a 45% relative risk reduction in morbidity and mortality at the 10 mg dose compared to placebo in patients with PAH that was mainly driven by a reduction in the worsening of PAH ($p<0.0001$) with no significant difference in the risk of death ($p=0.79$). Macitentan does not appear to increase survival but the pivotal study was not powered to assess this endpoint. Secondary endpoints on symptom relief such as improvements in 6MWD, WHO FC (74% higher chance of FC improvement at six months), quality of life, number of hospitalisations and days per year were supportive of the efficacy of macitentan 10 mg. The placebo subtracted change in 6MWD at six months was small at 22m (bosentan and ambrisentan ranged from 31 to 76m at three to four months) but statistically significant ($p=0.0078$) and appeared to be maintained at 12 months. Death due to PAH or hospitalisation due to PAH showed a relative risk reduction of 33% on 3 mg macitentan and 50% on 10 mg macitentan but due to the hierarchical testing procedures, no confirmatory claims could be made for 3 mg and the 10 mg result could only be considered a positive study and not a conclusive study. Subgroups analyses confirmed efficacy by WHO FC (but there were few patients with FC IV), PAH subtypes (but there were few with HIV, toxins or drugs), age (but there were only 13 subjects on either dose of macitentan in the 12 to < 18 years group) and concomitant PAH treatments (PDE5 inhibitors and mainly inhaled prostanoids).

Indication, WHO Group 1 subgroups and WHO Functional Class: The sponsor proposed an initial indication that has been modified by the clinical evaluator and then subsequently modified by the sponsor. The indication is long and includes endpoint claims, a description of disease progression, which combination PAH treatments and inclusion of subgroups of WHO Group 1 for which there was evidence from the submitted data. The wording approved in USA and recommended for approval in Europe capture similar subtypes of PAH but it is unclear if this implies it is approved for all subtypes of PAH or only those listed. Only WHO FC II-III appears to have been approved in USA and Europe. The indication here could be aligned with bosentan and ambrisentan which are simpler and place endpoint claims in the Clinical Trials section of the PI where they are better suited. The definition of disease progression is also better suited to the Clinical Trials section. The WHO Group 1 subgroups and WHO FC however need consideration. For WHO Group 1, the sponsor has identified those subgroups that were represented in the pivotal study, as part of the indication. Bosentan and ambrisentan have both been approved with specific subgroups included in the indication and therefore approving only those subgroups would be consistent with these other ERAs. This would approve only those subgroups which have clearly demonstrated efficacy such as idiopathic and familial PAH (57%), PAH associated with connective tissue disorders (31%) and PAH caused by congenital heart disease with repaired shunts (8%), although bosentan had a specific study to support the congenital heart disease group. PAH associated with drugs and toxins (3%) and HIV (1%, n=10) were small groups and it is unclear if these should be included in the indication or not given the limited data. There may also be other WHO Group 1 subgroups that could benefit but since they were not included in the data then further evidence would be needed. The similarities of the other subgroups in WHO Group 1 are unclear and there are groups such as persistent pulmonary hypertension of the newborn and pulmonary veno-occlusive disease (PVOD) which are different to the other subgroups.

The classification system has also changed and may continue to do so (for example, Appendix 1 and 2). ACPM's advice is requested on the inclusion of certain subgroups.

The issue of WHO FC concerns those patients in WHO FC IV. The submitted data are mainly in patients with WHO FC II-III with only 2% in Class IV. Both the USA and possibly EU have indicated it for patients with Class II-III. In Australia, both bosentan and ambrisentan have been approved with Classes II-IV. Despite the few patients in Class IV in the dossier, this may be best left to clinical judgement on whether continuing treatment in this group is appropriate given that patients would be worsening if they reached Class IV. ACPM's advice is requested on this matter.

Consideration is therefore needed on the inclusion/exclusion of WHO Group 1 subgroups, WHO FC IV, endpoint claims such as disease progression and its definition. Given these issues, a proposed indication could be as follows:

Opsumit, as monotherapy or in combination with approved PAH treatments (phosphodiesterase-5 inhibitors or inhaled prostanoids), is indicated for the treatment of:

- *idiopathic and heritable PAH*
- *PAH associated with connective tissue disorders or*
- *PAH associated with congenital heart disease(PAH-CHD) with repaired shunts*

in patients with WHO Functional Class II, III or IV symptoms

Adults/Paediatrics: The sponsor has applied for use in patients 12 to < 18 years old but the pivotal study only included 20 patients in this age group (seven on placebo, seven on 3 mg macitentan and six on 10 mg macitentan). Subgroup analysis indicated the primary efficacy endpoint result and safety results were generally consistent with the overall population. Given the similar efficacy and no significant safety issues, then it appears reasonable to allow use in this population given the seriousness of the disease, however a precaution should be added on the limited data and lack of data on growth and development.

Safety and RMP: The safety profile of macitentan 10 mg was generally acceptable and consistent with known safety issues with ERAs such as embryo-foetal toxicity, liver function abnormalities, decreases in haemoglobin and hypotension. The main risks identified appear to be decreases in haemoglobin which tended to occur in the first three months then stabilise and can be monitored and hypotension which were small except for those with severe renal impairment and can be regularly measured. Marked decreases in leucocytes and platelets were noted but mean decreases were small in all groups.

Data deficiencies: There is a lack of robust data in WHO FC IV, PAH subgroups other than connective tissue disease, idiopathic/heritable and congenital heart disease, use with other PAH treatments (such as epoprostenol) and in the paediatric age groups.

Request for further information

The sponsor is requested to address the following issues in the Pre-ACPM Response:

1. Are any further studies planned in specific subgroups of PAH that have not been fully covered at present or in any other subtypes of pulmonary hypertension?
2. Are any further studies or registries planned to examine serious hepatic risks with macitentan?
3. Please clarify if the approved indication in USA and that recommended for approval in Europe is for all subgroups of PAH or only those mentioned in the indications?
4. Discuss the efficacy and safety results for patients with PAH associated with drugs, toxins and HIV compared to the overall population results.

5. The outstanding RMP matters as discussed above.

Proposed action

The Delegate had no reason to say that the application for Opsumit should not be approved for registration.

The Delegate's suggested indication is as follows:

Opsumit, as monotherapy or in combination with approved PAH treatments (phosphodiesterase-5 inhibitors or inhaled prostanoids), is indicated for the treatment of:

- *idiopathic and heritable PAH*
- *PAH associated with connective tissue disorders or*
- *PAH associated with CHD with repaired shunts*

in patients with WHO Functional Class II, III or IV symptoms.

Conditions of registration

The following are proposed as conditions of registration:

- The implementation in Australia of the EU Risk Management Plan for Opsumit (macitentan), version 3, dated 12 August 2013 (DLP 26 April 2012), with the Australian Specific Annex, version 1.0, dated 22 August 2013, and subsequent changes as agreed from the sponsor email of 29 October 2013 and Pre-ACPM Response of 19 November 2013, included with submission PM-2012-04112-1-3, and any subsequent revisions, as agreed with the TGA.

Request for ACPM advice

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

1. Whether the data/justifications are sufficient to support registration for only specific subgroups of WHO Group 1 and whether it should include PAH associated with drugs, toxins and HIV; noting the change in classification system?
2. Whether the data/justifications are sufficient to support WHO FC II-IV or only FC II-III?
3. Whether the wording of the Indications should be simplified in relation to endpoint claims and disease progression definition and place this information in the Clinical Trials section of the PI instead.

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

Introduction

Evaluation reports associated with the Category 1 application for Opsumit (macitentan) submitted on 7 February 2013 were received from the TGA on 17 October 2013. Actelion has reviewed the reports, and are responding to errors documented, providing clarifications, and responding to questions raised. The location of the error, area requiring clarification, or question is provided along with a response to provide the correct information.

Clinical evaluation report

Upon review of the Clinical Evaluation Report the sponsor did not identify any important errors requiring correction.

Clinical comments to draft product information

Updates were implemented into the PI based on comments on the first round review and those documented within the Evaluation Reports.

Indication statement

The Applicant would like to propose the following modified Therapeutic Indication.

> *Opsumit, as monotherapy or in combination with approved PAH treatments (phosphodiesterase-5 inhibitors or prostanoids), is indicated for the long-term treatment of PAH) in patients of WHO FC II to IV to delay disease progression. Disease progression included: death, initiation of IV or SC prostanoids, or clinical worsening of PAH (decreased 6MWD, worsened PAH symptoms and need for additional PAH treatment). Opsumit also reduced hospitalisation for PAH.*
>
> *Efficacy was shown in a Phase III study in a PAH population that included patients with aetiologies of idiopathic PAH (55%), PAH associated with connective tissue disorders (31%), PAH associated with congenital heart disease with shunts (8%), familial PAH (2%), and PAH associated with other aetiologies [drugs and toxins (3%) and HIV (1%)] (see Clinical Trials).*

Sponsor justification

Justification for mentioning effects on disease progression and PAH-related hospitalisation in the Therapeutic Indication

The efficacy of macitentan in the long-term treatment of PAH is demonstrated by the results from SERAPHIN, the first study in PAH that used a clinical outcome composite primary endpoint, defined as morbidity-mortality in the protocol. The design and results of the study bring the documentation of treatment effects in the rare disease of PAH to a new level. Previous studies in PAH focused on symptomatic or exercise capacity improvement over a relatively short treatment period. The applicant is of the opinion that this differentiation should be emphasised in the Therapeutic Indication for Opsumit, in order to provide adequate information to the prescriber.

The primary clinical outcome endpoint of SERAPHIN was stringently defined as a composite of events each intended to identify clinically relevant, irreversible progression of PAH, and all events were adjudicated by the independent CEC. The study was powered for a conclusive result on the composite primary endpoint in the pre-specified time-to-first-event analysis.

The primary objective of the SERAPHIN study was achieved in accordance with the strict statistical requirements of the protocol. The Hazard Ratio (HR) versus placebo for a first morbidity-mortality event during treatment with macitentan 10 mg was highly statistically significant at 0.547 (97.5% CLs 0.392, 0.762, log rank $p<0.0001$). The 45% risk reduction versus placebo observed with macitentan 10 mg is highly clinically relevant. The absolute risk reduction corresponds to a low NNT of six patients to prevent one event (95% CLs 4.48, 10.80) at two years. The effect of macitentan 10 mg was consistent across patient subsets, including in patients with or without background PAH-specific therapy, as well as across WHO FC I/II and WHO FC III/IV subgroups. In all analyses, the effect of macitentan was established early and was sustained for the duration of the study. In the macitentan 10 mg group, 31.4% of patients experienced at least one primary endpoint

event, compared to 46.4% of patients in the placebo group. The most frequently first-reported event was a morbidity event. More placebo patients (39.6%) than macitentan 10 mg patients (24.8%) experienced a morbidity event. The proportion of patients with death as the first event was 6.6% in the macitentan 10 mg group, and 6.8% in the placebo group.

Landmark analyses

In order to gain further understanding regarding the clinical relevance/prognostic importance of experiencing a non-fatal primary endpoint event (essentially, 'other worsening of PAH') in SERAPHIN, so called landmark analyses were conducted [Anderson 1983[18]], looking at survival up to EOS (Kaplan-Meier estimates and Cox proportional hazards regression) for the populations of patients who had, or had not experienced an event prior to landmark time-points, and who were still alive at the respective time-point. Landmark time-points of three months, six months, and 12 months into the study were explored. A clear separation between survival curves for patients having or not having experienced an event was seen at all three time-points. The risk of death of all causes up to EOS was about 1.6 to 3.3 times higher in patients who had experienced a morbidity event up to the different landmark times, as compared to in patients who had not experienced an event [Table 10].

Table 10: Landmark analyses: Hazard ratio for death of all causes up to EOS by non-fatal morbidity event prior to Month 3, Month 6 and Month 12, All-randomised set

Variable	HR	HR 95% CL	Pr > ChisSq
Non-Fatal Event up to Month 3 (Yes versus No)	3.272	1.865 , 5.739	< 0.0001
Non-Fatal Event up to Month 6 (Yes versus No)	1.615	0.910 , 2.865	0.1014
Non-Fatal Event up to Month 12 (Yes versus No)	1.821	1.085, 3.055	0.0232

CL = confidence limit; HR = hazard ratio.
Adjusted for baseline PAH therapy and baseline WHO FC

Time-Varying Covariates (TVC)

The hypothesis that avoiding/delaying morbidity events as defined in SERAPHIN is of high relevance for vital outcome was further verified with a TVC analysis. This approach further supports the Landmark Analyses since it is based on the entire population and utilises all the information on any subject during the course of the study. This method incorporates morbidity events during the study as a TVC, while accounting for treatment within the context of the Cox's model for time to death up to EOS. The TVC results showed that the occurrence of a morbidity event, at any time during the SERAPHIN study, was strongly associated with the occurrence of death up to EOS (data on file: deviance=35; $\chi^{2(1)}$, p-value <0.0001).

These results jointly support a strong prognostic relevance of a morbidity event for death. This observation suggests that preventing morbidity events, as defined in the SERAPHIN protocol lead to a decrease in the risk of death and, thus, that these events strongly denote PAH disease progression.

[18] Anderson JR, Cain KC, Gelber RD. 1983. Analysis of Survival by Tumor Response. JCO Nov.1:710-719.

Survival analyses

The effect of macitentan 10 mg to reduce the risk of events of irreversible disease progression is also strongly supported by the consistent findings in survival analyses. In PAH, death is usually preceded by disease progression that can be identified as a morbidity event. A non-negligible number of deaths were not captured in the time to first event analysis because they were preceded by a primary morbidity event. As a consequence, the death component of the primary morbidity/mortality endpoint of SERAPHIN does not provide the complete or even the most important information needed to evaluate the survival benefit of macitentan in PAH. Instead, the assessment of the effect of macitentan on mortality needs to consider the entirety of the survival information collected in the study, as well as the consistency between different analyses.

Results of the mortality-related analyses of SERAPHIN are displayed in Table 11, and can be summarised as follows:

- Up to EOS, and despite the cross-over to macitentan 10 mg or alternative medication after a morbidity event (ITT analysis), the estimated risk reduction with macitentan 10 mg versus placebo was 23% for all-cause death.
- Up to EOT, the estimated risk reduction for death with macitentan 10 mg versus placebo was 36% for all-cause death

Table 11: Analyses on time to death up to EOS and up to EOT in SERAPHIN, All-randomised set

Endpoint	Period of assessment	Placebo N = 250	Macitentan 10 mg N = 242
Death (all causes)	**up to EOS**	n = 44	n = 35
HR (97.5% CLs),			0.771 (0.464, 1.282)
logrank p-value			p = 0.2509
Relative risk reduction			23%
Death (all causes)	**up to EOT**	n = 19	n = 14
HR (97.5% CLs),			0.638 (0.287, 1.418)
logrank p-value			p = 0.2037
Relative risk reduction			36%

Source: D 12.425. CL = confidence limit; EOS = end of study; EOT = end of treatment; HR = hazard ratio; PAH = pulmonary arterial hypertension.

Hospitalisation

Hospitalisation accounted for most of the events in the critical composite secondary endpoint of death due to PAH or hospitalisation for PAH up to EOT. The hazard ratio with the 10 mg dose of macitentan versus placebo was 0.50 (97.5% CI, 0.34 to 0.75; log rank p<0.001). The mean number of hospitalisation days per year (all causes) was 5.7 days in the macitentan 10 mg group compared to 12.2 days in the placebo group. The mean number of PAH-related days of hospitalisation per year was 3.8 days in the macitentan 10 mg group and 8.3 days in the placebo group. Macitentan decreased the PAH-related

hospitalisations by more than half. Hospitalisation is an important consequence of PAH progression and disease-related complications. A sustained treatment effect on this parameter has not been demonstrated with other PAH medicines.

Summary

The efficacy of macitentan has been comprehensively documented in a broad population of symptomatic PAH patients, both in monotherapy and in combination with other PAH-specific treatment. With the large and long-term SERAPHIN study it has been robustly and credibly shown for the first time that a PAH therapy, macitentan 10 mg, is effective in reducing the risk of irreversible disease progression and its complications in these patients while also providing symptomatic and functional benefit to patients. The proposed therapeutic indication is well supported by the data provided and the sponsor is of the opinion that the objectives of therapy achieved with macitentan should be included in the therapeutic indication as has been done with previously approved PAH therapies in Australia. The revised indication wording is in accordance with that approved by the US FDA.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Opsumit film coated tablet containing 10 mg of macitentan to have an overall positive benefit–risk profile for the delegate's amended indication;

> *Opsumit, as monotherapy or in combination with approved PAH treatments (phosphodiesterase-5 inhibitors or inhaled prostanoids), is indicated for the treatment of:*

- *idiopathic pulmonary arterial hypertension*
- *heritable pulmonary arterial hypertension*
- *pulmonary arterial hypertension associated with connective tissue disorders or*
- *pulmonary arterial hypertension associated with congenital heart disease with repaired shunts in patients with WHO Functional Class II, III or IV symptoms*

Specific advice:

The ACPM provided the following specifically requested advice:

1. Whether the data/justifications are sufficient to support registration for only specific subgroups of WHO Group 1 and whether it should include PAH associated with drugs, toxins and HIV; noting the change in classification system?

Macitentan is a new endothelin A and B receptor antagonist. In a randomised controlled trial the effects are clinically meaningful, although the mortality data was not significant. The safety profile of the medication is well recognised with this class of medication and there were no new safety issues identified in the pivotal efficacy study but longer term data needs to be collected.

Extension to patients with portal hypertension and persistent PHPT of the newborn, which are classed in Group 1, may have different pathophysiology and require further data for inclusion.

Therefore the committee advises that the indication should only include those subgroups of WHO Group 1 for which sufficient data have been provided. The indication proposed by the delegate that was consistent with other ERAs is acceptable.

2. Whether the data/justifications are sufficient to support WHO FC II-IV or only FC II-III?

The ACPM advised the inclusion of the FC IV group was acceptable. Although there are not many patients with severe disease in the studies, this is not surprising. The limited data suggest the sicker the patients were the greater benefit. These patients will be monitored by experienced clinicians in PAH prescribing centres and the use of macitentan in this group should be left up to the discretion of the treating clinician.

3. Whether the wording of the indications should be simplified in relation to endpoint claims and disease progression definition and place this information in the Clinical Trials section of the PI instead.

The ACPM;

- advised it would add clarity to separate idiopathic and heritable PAH
- agree with Delegate on the indication being in keeping with current bosentan entry
- agree with removal of claim re effect on morbidity and mortality from indication and inclusion of the percentage of each class of PAH enrolled and outcome measures descriptors to be placed in Clinical Trials section of PI
- it would accept the addition of the expression 'long term' prior to treatment only in the Clinical Trials section.

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Negotiation of PI and CMI to the satisfaction of the TGA.

Proposed Product Information/Consumer Medicine Information amendments:

The ACPM agreed with the delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- A statement in the *Precautions* section of the PI and relevant sections of the CMI should clarify that pregnancy is in itself a contraindication in PAH.
- The statement in the PI and relevant sections of the CMI on contraception should advise the use of two reliable methods of contraception and for the patient to discuss with their doctor or gynaecologist which methods would be most suitable for them.
- The PI should state that women should not become pregnant for 3 months following discontinuation, consistent with other endothelin receptor antagonists in Australia.
- Clear statements in the Clinical Trials section of the PI
  - to reference the pivotal study was not powered to assess effect on mortality
  - to reference the benefit on mortality was only seen in a combined endpoint analysis and no conclusive claims should be made.
- A statement in the *Clinical Trials* section of the PI on the lack of data on treatment in Group1 patients, (PAH secondary to drugs, toxins and HIV).

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of:

- Opsumit macitentan 10 mg film coated tablet bottle; and
- Opsumit macitentan 10 mg film coated tablet blister pack,

for once daily oral administration, indicated for:

Opsumit; as monotherapy or in combination with approved PAH treatments (phosphodiesterase-5 inhibitors or inhaled prostanoids), is indicated for the treatment of:

- *idiopathic pulmonary arterial hypertension*
- *heritable pulmonary arterial hypertension*
- *pulmonary arterial hypertension associated with connective tissue disease*
- *pulmonary arterial hypertension associated with congenital heart disease with repaired shunts*

in patients with WHO Functional Class II III or IV symptoms.

Specific conditions of registration applying to these goods

- The Opsumit (macitentan) EU Risk Management Plan (RMP), version 3, dated 12 August 2013 (DLP 26 April 2012), with the Australian Specific Annex, version 1.0, dated 22 August 2013, and subsequent changes as agreed from the sponsor email of 29 October 2013 and Pre-ACPM Response of 19 November 2013, including the addition of the US registry as an additional pharmacovigilance activity in the Australian Specific Annex, included with submission PM-2012-04112-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- The following studies must be submitted to the TGA, as soon as possible after completion:
    a. The final study report for the long-term prospective observational study (product exposure registry) to evaluate potential serious hepatic adverse events related to the use of macitentan, including an assessment and analysis of the adverse events.
    b. The Periodic Safety Update Reports must include a discussion of liver safety from the above product exposure registry or alternatively annual interim reports of results from this registry must be provided to the TGA.

Attachment 1: Product Information

The PI at the time this AusPAR was published is at Attachment 1. For the most recent PI please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2: Extract from the Clinical Evaluation Report

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