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RESEARCH**

APPLICATION NUMBER:
204410Orig1s000

OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Deputy Office Director Decisional Memo
NDA/BLA #	204410
Supplement #	
Applicant Name	Actelion Pharmaceuticals LTD
Date of Submission	October 19, 2012
PDUFA Goal Date	October 19, 2013
Proprietary Name / Established (USAN) Name	Opsumit/ (macitentan)
Dosage Forms / Strength	10 mg Tablet
Proposed Indication(s)	(b) (4)
Action:	Approval for treatment of PAH to delay disease progression

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
CDTL Review	Mary Ross Southworth, PharmD, 9/19/2013
Statistical Review	Jialu Zhang, 6/18/2013
Pharmacology Toxicology Review	William T Link, 8/26/2013 Mohammad Rahman, 3/15/2013 (Carcinogenicity)
CMC Review/OBP Review	Thomas Wong, 5/24/2013 (Chemistry) John Duan, 6/18/2013 (ONDQA Biopharmaceutics) Ramesh Sood, 8/21/2013 (Tertiary review)
QT	Moh Jee Ng, 3/25/2013
Clinical Pharmacology Review	Sreedharan Sabarinath, Dhananjay Marathe, Ping Zhao 6/29/2013
Pediatric and Maternal Health	Tammie Brent Howard, 6/25/2013
OSI	Sharon Gershon, 5/14/2013, 5/20/2013, 6/23/2013, 9/6/2013
Medical Officer Review	Maryann Gordon, 6/21/2013 and 7/25/2013
OSE/Hepatic Safety	John Senior, 9/9/2013
OSE/DMEPA	Kim DeFronzo, 6/14/2013 and 8/7/2013
OSE/DRISK	Jason Bunting, 7/2/13
Labeling	Sharon Mills, 9/9/2013 Zarna Patel, 9/11/2013
Division Director Review	Norman Stockbridge

OND=Office of New Drugs
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 CDTL=Cross-Discipline Team Leader
 OSE= Office of Surveillance and Epidemiology
 DEPi= Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management

I. Introduction

Macitentan (OPSUMIT) is an endothelin receptor antagonist (ERA) intended for the treatment of pulmonary arterial hypertension (PAH) in WHO Group I adults (b) (4). The proposed claim was (b) (4).

(b) (4). The approved Indication is “Treatment of PAH to delay disease progression.” Disease progression included: death, initiation of IV or SC prostanoids, or clinical worsening of PAH (decreased 6 minute walk distance, worsened PAH symptoms, and need for additional treatment). The Indication also states that macitentan also reduced hospitalization for PAH. Macitentan will be the third ERA approved for PAH; these drugs reduce pulmonary artery vascular resistance and pulmonary pressure, reducing right ventricular heart failure. The two other drugs, bosentan and ambrisentan, share macitentan’s teratogenic effect, necessitating restricted distribution, as well as its testicular toxicity and ability to cause anemia. Bosentan is hepatotoxic (as was sitaxsentan, an ERA approved in Europe, but subsequently withdrawn), and dealing with its hepatotoxicity was a component of its limited distribution, but ambrisentan appears to be free of this toxicity, as shown by its overall data, including an extensive rechallenge study. Macitentan is clearly less hepatotoxic than bosentan, and may indeed prove not to be hepatotoxic, but it has not yet been shown to be entirely free of this risk (discussed below).

In addition to the endothelin receptor antagonists, PAH is treated by prostaglandin/prostacyclin analogues (epoprostenol, treprostinil, iloprost) and phosphodiesterase-5 (PDE-5) inhibitors (sildenafil, tadalafil). All treatments have been shown to improve 6 minute walk distance (6MWD) and “clinical worsening,” usually a composite of death, lung transplant, PAH hospitalization, and symptomatic worsening (generally including worsening symptoms, exercise ability, need for additional therapy) in placebo-controlled studies of 12-16 weeks duration. Macitentan’s controlled study supporting approval was considerably longer than previous controlled trials of ERAs. PAH is a fatal illness, and the available treatments may well affect mortality, but showing this in a controlled study will be difficult, as a deteriorating patient cannot be denied available treatments, meaning there will be no untreated comparator group.

Macitentan has an elimination half-life of about 16 hours and its active metabolite, with about 20% of the potency of the parent, has a half-life of about 48 hours.

Macitentan is metabolized predominately by CYP450 3A4 and strong inhibitors approximately double parent blood levels and reduce active metabolite levels. A 5 mg tablet would be useful for patients needing to use such treatment, e.g. drugs for HIV.

II. Effectiveness

The evidence of macitentan’s effectiveness in PAH is derived from the SERAPHIN trial (Study with Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve cliNical outcomes), a randomized double-blind long-term comparison of placebo and two macitentan doses, 3 and 10 mg, in 742 patients with PAH WHO Group I [primarily idiopathic (about 57%), related to connective tissue disorder (about 31%), or related to congenital heart disease with repaired stents (8%)]. To be randomized patients had to be in WHO functional class (FC) II (52%), III (46%), or IV (2%), have mean pulmonary artery pressure > 25 mmHg with pulmonary capillary wedge pressure < 15 mmHg, and have a 6 MWD ≥ 50 meters at randomization. Patients were predominately female (77%), average age about 45 and primarily European or Asian. About 60% of patients were receiving a PDE-5 inhibitor at baseline and about 5% were receiving oral or inhaled prostanoids.

The primary endpoint was a composite, the time to occurrence, up to the end of treatment plus 7 days, of:

- Death or a treatment emergent event with a fatal outcome within 4 weeks of study treatment discontinuation
- Atrial septostomy or hospitalization for septostomy
- Lung transplantation or hospitalization for treatment
- Initiation of i.v. or s.c. prostanoids or hospitalization for such initiation
- Other worsening of PAH, requiring all 3 of:
 - $\geq 15\%$ decrease in 6MWD (confirmed by 2 measurements on separate days)
 - worsening of PAH (increased WHO FC or no change in people already FC IV; or worsened R CHF not responsive to oral diuretics)
 - need for new PAH Rx, including one of the oral or inhaled prostanoids, new oral PDE-5 inhibitor, ERA after stopping study treatments, IV diuretics

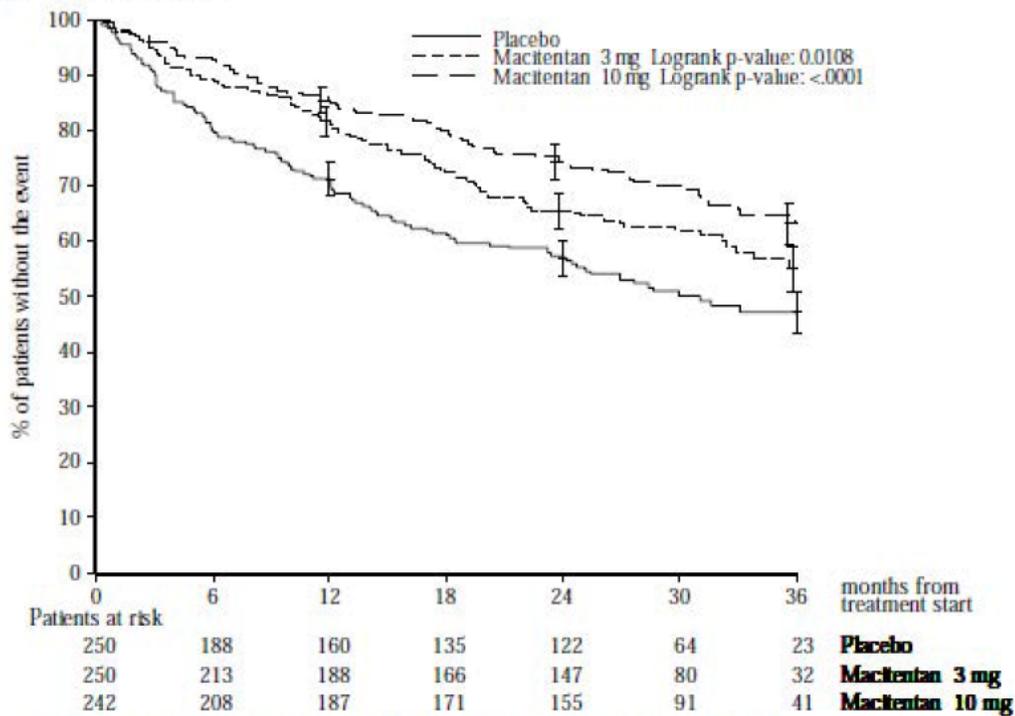
All of the above were subjected to blinded adjudication, including whether a death was PAH-related. Results were similar, however, when investigator reported events were analyzed.

The results for patients with a primary morbidity or mortality endpoint, and the components of the primary endpoint (there were no atrial septostomias) are shown in the following table:

	Placebo	Macitentan 3 mg	Macitentan 10 mg
	N = 250	N = 250	N = 242
	n (%)	n (%)	n (%)
Any primary event	116 (46.4)	95 (38.0)	76 (31.4)
	-----	p = 0.01	HR 0.55 (97.5 CI 0.39-0.76); p < 0.0001
Worsening PAH	93 (37.2)	72 (28.8)	59 (24.4)
Death, any cause	17 (6.8)	21 (8.4)	16 (6.6)
IV/SC Prostanoid	6 (2.4)	1 (0.4)	1 (0.4)
Lung Tx	0	1 (0.4)	0

The Kaplan-Meier curve for the results shows early separation of the 10 mg and placebo treatments with a persistent advantage over time. Median treatment durations were about 2 years.

Time to first confirmed morbidity/mortality event up to EOT+7 days (CEC) (Kaplan-Meier estimate with standard error bars)
 Analysis set: All-randomized



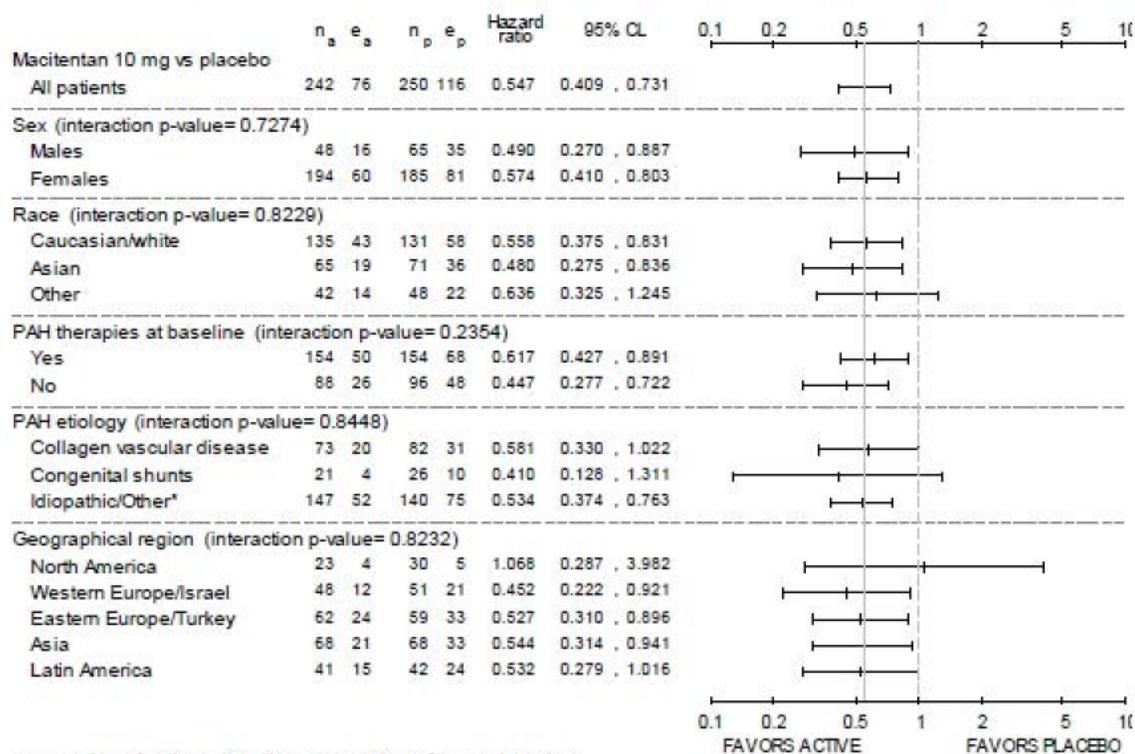
CEC = Clinical Event Committee, EOT = End of treatment. Events confirmed by Independent CEC.
 Survival plots are presented up to 36 months, time at which more than 10% of the patients are still in follow-up.
 Statistical tests are performed including all data available during the follow-up period.
 Figure MMTBG_A - Produced by (b) (4) on 29MAY12 - Data dump of 26APR12

Although the 3 mg dose was statistically significantly superior to placebo, it was clearly inferior to the 10 mg dose, with no compensating safety advantage, and will not be considered further.

It is often useful to examine events after the primary event (e.g., death would usually follow worsening of PAH) but disease progression led to open label macitentan in 32% of placebo patients and 21% of macitentan 10 mg patients, which would tend to diminish late differences and make interpretation difficult.

Results were consistent across subgroups, (b) (4)

Forest plot for time to first morbidity/mortality event (HR and 95% CL) - exploratory subgroup analysis
 Analysis set: All-randomized



n_a = number of patients in active; e_a = number of events in active

n_p = number of patients in placebo; e_p = number of events in placebo

*Other etiology consists of idiopathic or familial PAH, or PAH related to HIV infection or drugs and toxins.

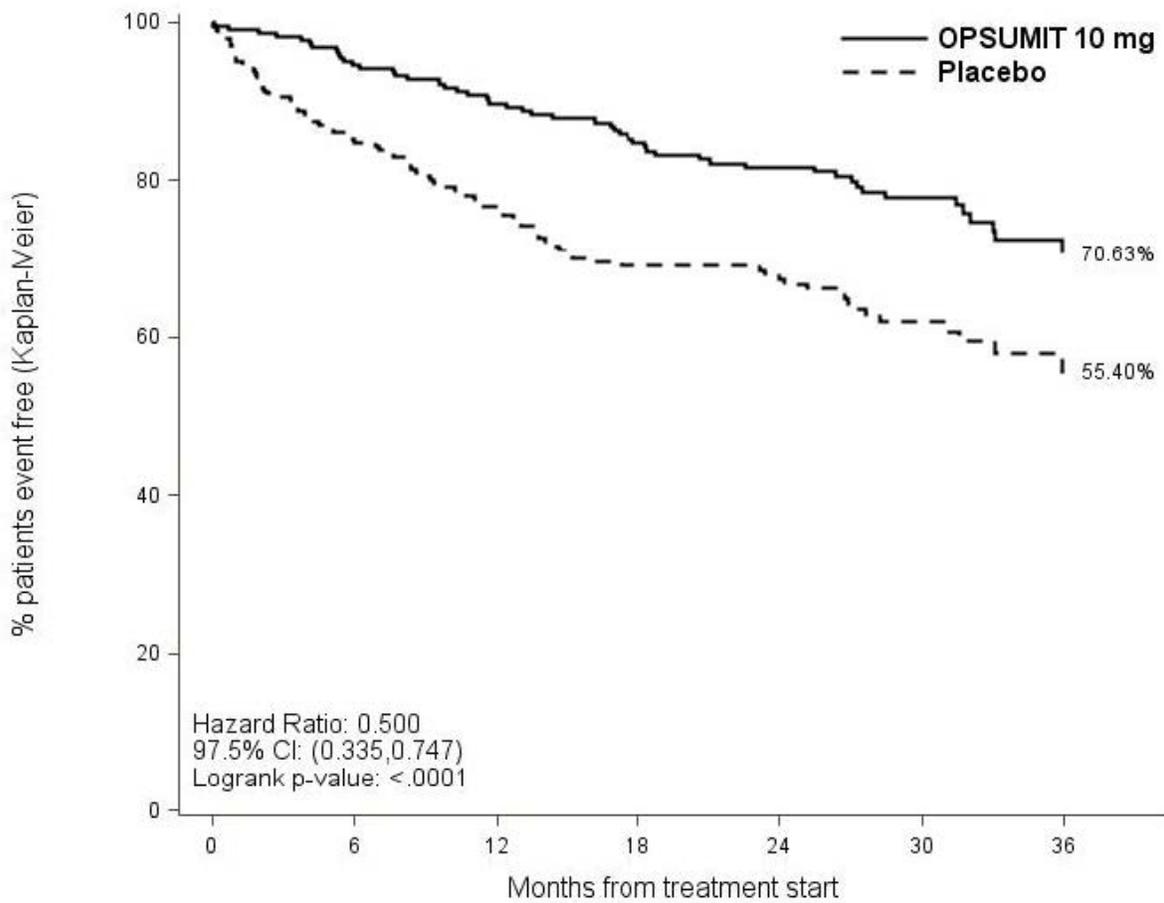
Figure MMT_HR_SG_A- Produced by (b) (4) on 26APR12 - Data dump of 26APR12

Notably, effect appeared present in men and women, Caucasians and Asians, patients on and not on other treatment, patients over and under 65 years of age, patients with various etiologies of PAH, and patients with varying degrees of impairment at baseline. The ability to show a risk reduction in both patients on no other treatment (HR 0.45) and on PDE-5 inhibitors (HR 0.62), i.e. an additive effect, discussed at length by Dr. Stockbridge and shown as Kaplan-Meier curves in Dr. Gordon's review (p 113, 114), is an important finding. The only subgroup with HF > 1 was the North American group, but there were only 9 events in that group, so that the observation is not interpretable.

Several secondary endpoints were evaluated, one of which was time to first occurrence of PAH death or PAH hospitalization (time on treatment plus 7 days). The results of this analysis are shown in the table below and in the Kaplan-Meier curve that is provided in labeling.

	Placebo (N=250) n (%)	OPSUMIT 10 mg (N=242) n (%)
Death due to PAH or hospitalization for PAH	84 (33.6)	50 (20.7)
Component as first event		
Death due to PAH	5 (2.0)	5 (2.1)
Hospitalization for PAH	79 (31.6)	45 (18.6)

Kaplan-Meier Estimates of the Occurrence of Death due to PAH or Hospitalization for PAH in SERAPHIN

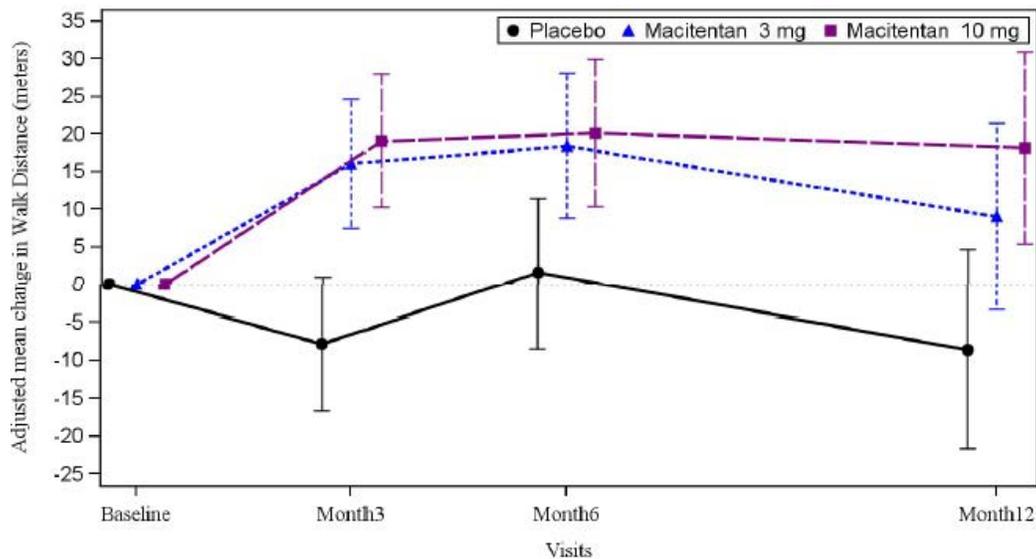


Number at risk							
OPSUMIT 10 mg	242	203	183	166	152	86	39
Placebo	250	188	155	132	119	62	22

This finding appears important enough to include in labeling, although it is not surprising, given the effect on PAH worsening. There was a favorable trend on mortality in the overall study (not for the first event) but it did not reach statistical significance, perhaps because people doing badly were treated with various therapies, including macitentan. Deaths from all causes at the end of the study, after many patients were receiving open-label macitentan, were fairly similar in the placebo (18%) macitentan 3 mg (19%), and macitentan 10 mg (14%) groups.

There was also a persistent effect on 6MWD of about 20 meters.

Plot of adjusted mean (95% CL) changes from baseline in Walk Distance values (meters) by visit up to Month 12
Analysis set: All-randomized



95% confidence limits of adjusted mean are displayed.

All in all, macitentan has more long-term controlled data than any previously approved PAH treatment. There was a clear and persistent effect on symptoms (worsening) and hospitalization for PAH.

III. Safety

Safety is extensively discussed in reviews by Drs. Gordon and Southworth. Like other endothelin receptor antagonists, macitentan is an animal teratogen and will have a REMS linking dispensing to mandatory monthly pregnancy testing and use of adequate contraception in women of childbearing potential, similar to programs for bosentan and ambrisentan.

Liver toxicity for bosentan is clear and appears reasonably well managed with monthly testing. Ambrisentan no longer (after reassuring post-marketing data) bears any liver monitoring instructions. Labeling also cites a 34 patient rechallenge study in which patients with hepatotoxic responses to bosentan or another ERA (8 of whom had a rechallenge, all of them positive), in which only 1 had any hepatotoxic response at all (and it did not recur when the drug was given again).

In SERAPHIN and phase 2 studies, rates of AT and bilirubin elevations were as follows: (CDTL review)

	Macitentan		Placebo
	3 mg n = 311	10 mg n = 423	1 n = 370
ALT/AST > 3 ULN	3.6%	3.1%	3.9%
AST/ALT > 8 ULN	1.4%	1.4%	0.6%
Total Bili > 2x ULN	6.0%	5.0%	10.6%
AST/ALT > 3x and TBil > 2x, any time	1.7%	1.3%	1.4%

In examining the 12 (2 placebo) cases in which there was both elevated AT (> 3x ULN) plus elevated bilirubin (to > 2x) ULN cases, Dr. Senior (review 8/15/13) found that all but one had alternative explanations (bilirubin elevated at baseline, right heart failure, acute viral hepatitis, respiration failure, pancreatic carcinoma). Even in the absence of “clean” cases of hepatotoxicity, however, exposure is relatively limited, so that the sponsor will be required to conduct a post-marketing registry to provide further assessment. There will be, however, no suggested liver monitoring.

Anemia was observed in 11% of patients on macitentan 10 mg vs 2% on placebo and mean Hg was 1 g/dL lower on macitentan compared to placebo, a finding similar to other ERAs.

Like other ERAs, animal data suggest testicular toxicity, probably reversible, with effects on spermatogenesis and sperm quality. Although there are no macitentan human data, labeling will warn about this.

IV. Conclusion

Macitentan is an ERA that at a dose of 10 mg provides a sustained beneficial effect in delaying time to clinical worsening of PAH. It also lowered the rate of hospitalization for PAH. It will be delivered under a system that protects against fetal exposure (it is a teratogen like other ERA's) and will have a post-approval registry to examine possible hepatotoxicity. Although pre-marketing data do not clearly indicate hepatotoxicity, labeling will state that liver enzyme tests need to be obtained prior to macitentan initiation but it calls for repeat tests only if clinically indicated, i.e. not routinely.

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/s/

ROBERT TEMPLE
10/18/2013