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APPLICATION NUMBER:

204410Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	September 19, 2013
From	Mary Ross Southworth, PharmD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 204410
Applicant	Actelion Pharmaceuticals LTD
Date of Submission	October 19, 2012
PDUFA Goal Date	October 19, 2013
Proprietary Name / Established (USAN) names	OPSUMIT
Dosage forms / Strength	10 mg tablet
Proposed Indication(s)	(b) (4)
Recommendation:	*Approval for reduction in risk of PAH related death and hospitalization from PAH*

Materials Reviewed	**Review Author/Date**
CMC	Thomas Wong, 5/24/2013 (Chemistry) John Duan, 6/18/2013 (ONDQA Biopharmaceutics) Ramesh Sood, 8/21/2013 (Tertiary review)
Pharmacology Toxicology	William T Link, 8/26/2013 Mohammad Rahman, 3/15/2013 (Carcinogenicity)
Clinical Pharmacology	Sreedharan Sabarinath, Dhananjay Marathe, Ping Zhao, 6/29/2013
QT	Moh Jee Ng, 3/25/2013
Clinical	Maryann Gordon, 6/21/2013 and 7/25/2013
Statistical	Jialu Zhang, 6/18/2013
OSE/Hepatic Safety	John Senior, 9/9/2013
OSE/DRISK	Jason Bunting, 7/2/ 2013
OSE/DMEPA	Kim DeFronzo, 6/14/2013 and 8/7/2013
OSI	Sharon Gershon 5/14/2013, 5/20/2013, 6/3/2013, 9/6/2013
Pediatric and Maternal Health	Tammie Brent Howard, 6/25/2013
Labeling	Sharon Mills, 9/9/2013 Zarna Patel, 9/11/2013

1. Introduction

Actelion Pharmaceuticals submitted NDA 204410 seeking approval to market macitentan for the long-term treatment of pulmonary arterial hypertension (PAH, WHO Group I) in adult (b) (4) The application relies on the results of a single large multicenter, randomized, double-blind, placebo-controlled

trial, SERAPHIN (Study with Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve cliNical outcome) to support the efficacy and safety of macitentan for this indication.

PAH is characterized by restricted flow through the pulmonary arterial vasculature, increased pulmonary vascular resistance, and, ultimately, right ventricular heart failure. Contributing causes are thought to include an imbalance in vasoconstrictive/vasodilatative homeostatic mechanisms and abnormal cellular proliferation. Approximately 15 million people are afflicted with the disease and one year survival is approximately 85% with modern therapy. Currently approved drug therapy for PAH WHO Group 1 (a PAH subset with etiologies including familial, idiopathic, connective tissue disease) include prostaglandin/prostaglandin analogues (epoprostenol, treprostinil, ilopost), phosphodiesterase-5 inhibitors (sildenafil, tadalafil), and endothelin receptor antagonists (ERAs). These agents have been shown to have effects on the symptoms of the disease (improvement in exercise ability, delay clinical worsening), but there is little information to support much of an effect on mortality risk.

Macitentan is an orally administered ERA and prevents endothelin-1 (ET-1) from binding to its receptors (ET_A and ET_B). ET-1 is thought to play a pathogenic role in PAH (vasoconstriction); concentrations of ET-1 have been found to be elevated in the plasma and lung tissue of patients with PAH. Macitentan has been shown to decrease mean pulmonary arterial pressure in animal and human models of pulmonary hypertension.

Two other ERAs are approved in the US for patients with PAH WHO Group 1, ambrisentan (2007) and bosentan (2001). Both have demonstrated beneficial effects on 6 minute walk distance (6MWD) and clinical worsening (typically a composite of death, transplantation, PAH hospitalization, worsening symptoms of PAH/exercise ability or need to add new therapy) in short term studies (12-16 weeks duration). The clinical worsening benefit in both drugs' programs was largely driven by effects on symptoms and added drug therapy, not mortality or hospitalization. The safety profiles of the two drugs are similar (teratogenicity, testicular toxicity, anemia) with the exception of hepatotoxicity; a significant safety issue for bosentan (and sitaxsentan, an ERA once approved in Europe, not in the US), but not ambrisentan.

2. CMC/Device

Drug Substance

Macitentan drug substance is a new molecular entity that is (b) (4) a white crystalline powder that is not soluble in water. The molecule is achiral and the manufacturing process yields its most stable form, (b) (4) The drug substance is manufactured using (b) (4) . Twelve-month stability data (at room temperature/humidity, in proper containers) supports (b) (4) retesting.

Drug Product

The drug substance is [redacted] (b) (4) The drug product is manufactured by [redacted] (b) (4) The proposed to-be-marketed product is a film-coated, immediate release tablet in one strength, 10 mg, containing standard excipients. The provided stability data support a 24-month expiration period for this product.

The CMC reviewers concluded that the applicant's proposed manufacturing (and associated analytic methods) of the drug product and drug substance are acceptable. The overall EES status of the manufacturing sites is pending.

3. Nonclinical Pharmacology/Toxicology

Macitentan is an orally active ERA that inhibits the binding of endothelin-1 to both ET_A and ET_B receptors with an inhibitory potency ratio of 50:1. Its one active metabolite, ACT-132577, is also a dual receptor antagonist, but, *in vitro*, demonstrates much less potent inhibition on each receptor than does the parent.

In rats with PAH, reductions in mean pulmonary arterial pressure were observed without effects on systemic blood pressure. After several weeks of treatment, macitentan appeared to have an inhibitory effect on pulmonary vascular remodeling and right ventricular hypertrophy.

Given the safety profiles of other members of the class, the toxicologic findings with regard to hepatotoxicity, red blood cell parameters, reproductive toxicity, and testicular toxicity are of particular interest.

Hepatotoxicity

Hepatic findings in animals were limited to increased liver weight and centrilobular hypertrophy (mice, rats, dogs in all dose groups). Focal liver necrosis was observed in rats with chronic administration (13 week) of a high dose and was accompanied by high morbidity.

Reviewer comment: Focal liver necrosis is a fairly non-specific finding with this dosing pattern and may not predict actual hepatotoxic activity in humans. As with ambrisentan and bosentan, there is little evidence for hepatic injury based on the toxicology findings.

Testicular Toxicity

Chronic macitentan administration was associated with dilation of seminiferous tubules in rats and dogs. These changes were rare, low in severity, and appeared to be reversible. Abnormal sperm (reversible and without evidence of histological changes in the testes) were observed in a 26-week rat toxicity study.

Reviewer comment: Similar findings were observed with bosentan and ambrisentan. A human study in bosentan suggests that it may have significant effects on sperm count in some patients. A human study of the effects of macitentan on spermatogenesis and sperm quality was attempted with macitentan but was uninterpretable because of an error in treatment

allocation. The primary reviewer recommends that macitentan be labeled for the potential for testicular toxicity (like bosentan and ambrisentan) and I concur.

Red Blood Cell Parameters
Dose-related, reversible decreases in hematocrit, RBC, and hemoglobin concentration were observed in most rat and dog studies.

Reproductive Toxicity
There were generally no effects observed on male and female fertility, although there was an increased incidence of early intrauterine deaths and post-implantation loss on dames mated to exposed male rats.

Fetal developmental effects were evaluated in rats and rabbits. Serious malformations were observed at all doses tested and comprised craniofacial abnormalities and cardiovascular abnormalities. The NOAEL for embryo-fetal development was not established for either species.

Other toxicology findings:
There was no evidence of genotoxicity or mutagenicity observed with macitentan. The carcinogenicity studies were considered negative by the Executive Carcinogenicity Assessment Committee (CAC).

4. Clinical Pharmacology/Biopharmaceutics

Pharmacokinetics
The pharmacokinetics of macitentan is dose proportional from 1 to 30 mg. Cmax is reached by about 8 hours after oral dosing. One active metabolite (ACT-132577- with less potency on the ET_A receptor and ET_B receptor compared to macitentan) and one inactive metabolite (ACT-373989) were studied (several other inactive metabolites were identified). Macitentan and its active metabolite are highly protein bound (the metabolite less so than the parent). Macitentan undergoes metabolism by CYP3A and to a minor extent by CYP2C19. The apparent elimination half-life of macitentan and its active metabolite are approximately 16 and 48 hours, respectively. When radiolabeled drug is administered to healthy subjects, approximately 50% is recovered in urine and about 24% is recovered in feces.

There is no effect of food on absorption of the drug. Age, sex, body weight and race had no significant effect on exposure. Renal and hepatic impairment affect exposure (increased exposure in renal impairment and decreased exposure in hepatic impairment), but the changes are not considered clinically significant and do not require dose adjustment. Of note, patients with moderate to severe hepatic impairment were not studied in the pivotal trial.

Drug interactions
In vitro studies demonstrate that macitentan, at therapeutic doses, would not be susceptible to drug interactions via P-glycoprotein, OATP, or CYP enzymes, other than CYP3A.

In vivo studies identified clinically significant drug interactions. Rifampin, a strong CYP3A inducer, reduced exposure to macitentan by 80%. A single dose of ketoconazole, a strong CYP3A inhibitor, significantly increases exposure to macitentan (AUC 2.3-fold; Cmax 1.3-fold). A further increase in exposure with multiple doses of ketoconazole is expected based on PBPK modeling. PBPK modeling also suggests that chronic co-administration of ritonavir (strong CYP3A inhibitor) would result in 3- to 4-fold the exposure of macitentan alone. Because it is not well characterized, the model did not take into account the potential CYP3A induction qualities of ritonavir.

The pharmacology reviewers recommend avoiding co-administration of macitentan with rifampin (and other strong CYP3A inducers). Co-administration of macitentan with strong CYP3A inhibitors (ketoconazole, as well as HIV drug regimens containing ritonavir) should also be avoided.

Othe*r in vivo* drug interaction studies with sildenafil, warfarin, and cyclosporine did not demonstrate any significant impact on exposure to either macitentan or the co-administered drug.

QT study

A thorough QT study with macitentan 10 and 30 mg was designed and conducted adequately to exclude clinically significant effects on the QTc interval.

Dose considerations

Dose selection for the phase 3 study was based on findings from a phase 2 study in patients with essential hypertension. In this study, exposures associated with macitentan 3 and 10 mg were close to the plateau for blood pressure reduction and resulted in higher plasma levels of ET-1 than the comparators (0, 0.3, and 1 mg macitentan, dose-response was observed for blood pressure and ET-1 level). Therefore, the sponsor studied 3 mg and 10 mg in the pivotal PAH study.

The sponsor submitted PK data from a subset of patients in the study; however this subset had a significantly lower event rate than the total population (PK samples were collected at the end of treatment) and therefore a formal concentration-response analysis for efficacy or safety was not possible.

5. Clinical Microbiology

Not applicable

6. Clinical/Statistical- Efficacy

A single pivotal study, SERAPHIN (Study with Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve cliNical outcomes), was submitted to support the efficacy of macitentan in PAH. SERAPHIN was a double blind, placebo-controlled, parallel design, study in which 742 subjects with PAH WHO Group 1 (idiopathic, familial, related to collagen

vascular disease, repaired cardiovascular congenital abnormalities, HIV) were randomized 1:1:1 to macitentan 3 mg, macitentan 10 mg or placebo. Important inclusion criteria were:

- Functional Class (FC) II-IV
- Mean pulmonary arterial pressure >25 mm Hg with pulmonary capillary wedge pressure <15 mm Hg
- 6-minute walk distance (6MWD) ≥ 50 meters at screening and randomization

The primary efficacy endpoint was time to first occurrence up to end of therapy of the following:

- Death
- Atrial septostomy
- Lung transplantation
- Initiation of IV or SC prostanoids
- Other worsening of PAH, defined by the presence of all three of the following:
    - Sustained decrease in 6 MWD of at least 15% from baseline (confirmed by 2 6MWD performed on separate days)
    - Worsening of PAH symptoms or right heart failure
    - New treatment for PAH

The study was designed as an event driven trial with planned collection of 285 primary events. Subjects were followed for the primary events until end of therapy (EOT) + 7 days. Numerous secondary endpoints were described including change in 6MWD from baseline to month 6, improvement in FC, time to PAH death or PAH hospitalization, and time to all cause death.

Most subjects had idiopathic PAH (57%) or connective tissue disease (31%), most were FC II or III (98%) at baseline. Therapy for PAH was present at baseline for 64% of patients of whom 90% were on sildenafil.

About 80% of subjects completed the study. Patients who prematurely discontinued double-blind treatment could switch to open label macitentan 10 mg or other available therapy until end of study (EOS). More patients in the placebo group discontinued study treatment compared to either macitentan group (59% vs. 44% in macitentan 10 mg and 47% in macitentan 3 mg). The primary reason was disease progression leading to open-label therapy which occurred more frequently in the placebo group (32% vs. 21% in the macitentan 10 mg and 23% in macitentan 3 mg). Drop-outs for other reasons were well-balanced among the groups.

All primary endpoint events were adjudicated blindly by an independent committee. If the required assessment for an "other worsening PAH" event was not available (mostly when two qualifying 6MWD were not obtained), the committee would adjudicate and if confirmed the event was included in the primary analysis. Of the 341 morbidity/mortality events in the study, in 69 there were initial disagreements on the committee about confirmation of the event; in 20 of these events the committee could not reach consensus on confirmation. A sensitivity analysis in which patients without two qualifying 6MWD (n=54) were censored at the time of the event did not change the overall conclusion of the study.

Primary endpoint

For the primary endpoint, the HR for macitentan 10 mg vs. placebo was 0.55 (97.5% CI 0.39 to 0.76, p<0001) and for macitentan 3 mg vs. placebo was 0.70 (97.5% CI 0.52 to 0.96).

Table 1. Summary of causes of primary endpoint events (CEC-confirmed), all randomized set, End of treatment +7 days.

	Placebo N=250 No.	%	Macitentan 3 mg N=250 No.	%	Macitentan 10 mg N=242 No.	%
Total PATIENTS with at least one confirmed event	116	46.4%	95	38.0%	76	31.4%
First confirmed event						
WORSENING OF PAH*	93	37.2%	72	28.8%	59	24.4%
DEATH	17	6.8%	21	8.4%	16	6.6%
IV/SC PROSTANOID INITIATION	6	2.4%	1	0.4%	1	0.4%
LUNG TRANSPLANTATION	-		1	0.4%	-	

* Corresponds to 'Other worsening of PAH'
CEC = Clinical Event Committee, EOT = End of treatment.
Events confirmed by Independent CEC.
Source: Table 89

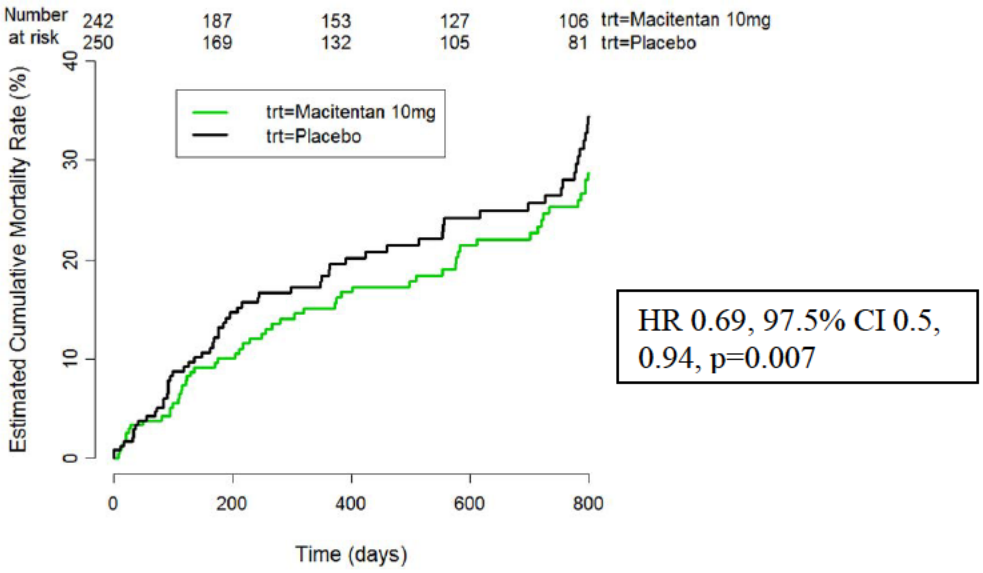
Macitentan has no apparent effect on overall mortality. The beneficial effect on the primary endpoint is largely driven by worsening of PAH (primarily deterioration in 6MWD and need for new PAH therapy).

Secondary endpoints

Macitentan significantly decreased the time to death due to PAH (adjudicated) or PAH hospitalization (not adjudicated) compared to placebo. When examining individual components, PAH death through end of therapy trended in the right direction for macitentan 10 mg vs. placebo without statistical significance; PAH death in the 3 mg group was the same as placebo. PAH death through EOS was not different between the groups.

	Placebo N=249	Macitentan 10 mg N=248	Macitentan 3 mg N=242
Time to death due to PAH or PAH hospitalization (# events, HR vs placebo, 97.5% CI)	84	50 0.5 (0.34, 0.75)	65 0.67 (0.46, 0.97)
Death due to PAH (EOT + 7 days)	14	7 0.44 (0.156, 1.248)	14 0.87 (0.373, 2.037)
Death due to PAH (EOS)	28	26 0.90 (0.489, 1.66)	30 1.05 (0.583, 1.893)
PAH hospitalization (patients with at least one)	82 (33%)	49 (20%)	58 (23%)

Fewer patients were hospitalized for PAH in the macitentan 10 mg group compared to placebo, however, this was not an adjudicated endpoint. To explore further macitentan's effect on hospitalization, the statistical reviewer analyzed time to first hospitalization for any cause (email from Jialu Zhang, 8/16/2013).



The reviewer was skeptical of the sponsor's presentation of data on annualized hospital days[1] for any cause (mean number per year 12 in placebo, 8 in macitentan 3 mg, and 6 in macitentan 10 mg). The presence of several outliers with extremely long hospital stays (>300 days) exaggerates the effect of macitentan. When she performed an analysis that eliminated 5 outliers with over 150 days in the hospital, the difference between macitentan 10 mg and placebo reduces from 6 days to < 4 days. Although the data trend in the right direction, she was unable to objectively determine if the difference was significant.

Reviewer comment: Macitentan 10 mg had a significant effect on the secondary endpoint, time to death due to PAH or hospitalization for PAH. The data suggest that macitentan 10 mg may also have a beneficial effect on all-cause hospitalization; however, this was not a prespecified endpoint.

At 6 months, both macitentan 3 mg and 10 mg showed significant effects on 6MWD and improvement in FC compared to placebo (see Table) supporting macitentan's effect on clinical worsening. The change in 6MWD (placebo corrected mean change of 22 meters with the 10 mg dose at 6 months) is consistent with effects observed with (lower doses of) other ERAs.

Subgroups

[1] Table 151, SERAPHIN study report

The results are consistent across subgroups by demographics, PAH etiology, and disease severity. The statistical reviewer notes an unfavorable trend for macitentan in the US.

Reviewer comment: The US/non-US finding is difficult to interpret because of the small number of events in the US. As the statistical reviewer notes, the event rate in the US is markedly lower in the US vs. non-US, perhaps reflecting different standards of care around the world. We have seen similar differences in other PAH development programs.

Macitentan's beneficial effect on the primary endpoint is consistent whether background PAH therapy is present at baseline or not, although the magnitude of effect appears lower in patients on background therapy.

To Be Marketed Dose

The sponsor has chosen to only market the 10 mg dose and provides the following rationale:

> *"…a stronger and highly statistically significant and clinically relevant reduction in the risk of occurrence of a morbidity or mortality event during treatment was achieved with macitentan 10 mg dose compared with the 3 mg dose…only macitentan 10 mg showed a consistent treatment effect across subgroups that included patient with or without background PAH therapy and WHO FC I/II versus WHO FC III/IV at baseline. These findings corroborate the stronger effect of 10 mg macitentan seen in the primary analysis, supporting the fact that this dose provides a more consistent benefit for long-term clinical outcome."*[2]

Reviewer comment: The sponsor should be encouraged to develop a lower strength tablet that could be co-administered with strong CYP 3A inhibitors and result in acceptable exposure.

7. Safety

The safety profile for macitentan is similar to that of previously approved ERAs and is largely based on pre-clinical data (teratogenicity, testicular toxicity) or what are considered class effects (pulmonary edema in patients with pulmonary veno-occlusive disease). Dose-related reductions in hemoglobin were observed in the pivotal trial.

Reviewer comment: These risks will be described in labeling. Macitentan should be contraindicated in pregnancy (Boxed Warning) and should be approved with a Risk Evaluation and Mitigation Strategy (REMS) that links drug dispensing to mandatory monthly pregnancy testing and use of adequate contraception in females of reproductive potential—similar to the REMS programs for ambrisentan and bosentan.

Hepatotoxicity and liver failure are associated with use of bosentan in PAH. Ambrisentan was assumed to have the same (class) effect upon its approval (and was labeled similarly to/had the same risk management as bosentan) even though the controlled trial data did not suggest any

[2] Summary of Clinical Efficacy, section 4.2.

significant imbalance in elevated transaminases. After accumulation of several years of reassuring post-marketing data, the labeling and risk management program for ambrisentan were altered to remove the warning/mandatory monthly liver monitoring for the product. Another ERA, sitaxsentan, was approved in EMA in 2006 but was subsequently withdrawn because of post-marketing cases of (sometimes fatal) liver toxicity that occurred despite regular monitoring of liver tests and prompt discontinuation of the drug when elevated transaminases were detected. An NDA for sitaxsentan was under review by the FDA at the time and the sponsor withdrew the application (b) (4)

The sponsor asserts that there is "no definite hepatotoxicity signal from macitentan"[3]. The abnormalities observed in all double blind, placebo-controlled phase 2 or 3 studies for each dose group is shown below (does not include data from the ongoing studies in ischemic digital ulcers or the open label portion of SERAPHIN).:

Laboratory abnormality	Macitentan				
	< 3 mg	3 mg	10 mg	All	Placebo
	N = 129	N = 311	N = 423	N = 863	N = 370
ALT / AST > 3 × ULN	3/125 (2.4%)	11/307 (3.6%)	13/414 (3.1%)	27/846 (3.2%)	14/360 (3.9%)
ALT /AST > 3 × ULN and TBIL > 2 × ULN at any time	0	5/301 (1.7%)	5/398 (1.3%)	10/824 (1.2%)	5/349 (1.4%)
ALT / AST > 8 × ULN	1/125 (0.8%)	4/307 (1.3%)	6/414 (1.4%)	11/846 (1.3%)	2/360 (0.6%)
TBIL > 2 × ULN	0	18/301 (6.0%)	20/398 (5.0%)	38/824 (4.6%)	37/349 (10.6%)

Analysis set: All treated; only patients with post-baseline assessments were counted.
NOTE 1: Denominator for percentages based on number of non-missing observations for each treatment group and total. Incidence based on the number of patients with at least one post-baseline abnormality for each category.

The hepatology reviewer assessed the hepatic findings submitted by the sponsor, including review of 12 cases meeting the laboratory criteria for Hy's law. He notes the following:

- Macitentan is structurally similar to bosentan but it is unknown if the hepatotoxicity risk is related to structure.
- There is a modest predominance of cases [meeting the laboratory criteria for Hy's law] among patients on macitentan (5/423 on 10 mg, 5/311 on 3 mg, 2/371 on placebo).

Reviewer comment: 3 placebo cases are not counted because total bilirubin was elevated at baseline (2) or not verified (1).

- Of the 12 Hy's law cases reviewed, only one case (67 year old Israeli female) could be assessed as possibly or probably caused by idiosyncratic response to macitentan.
- This experience is "no reassurance at all that if macitentan is approved as a safer hepatotoxicity alternative to bosentan that serious liver injuries will not occur in rare individuals as thousands of patients are treated, and perhaps less carefully observed for liver test abnormalities."

[3] Hepatobiliary Safety Report, 9/2012

He advises that an ideal approach to managing potential hepatotoxicity would involve daily symptom checks by the patient and prompt reporting of early symptoms to the physician so that appropriate diagnosis/treatment/drug discontinuation can be initiated early, particularly with confirmation of liver injury with serum testing.

Approaches to risk management for hepatotoxicity have been discussed among the review team members in the Divisions of Epidemiology II and of Risk Assessment in the Office of Surveillance and Epidemiology. That team does not believe a REMS is currently warranted for mitigating the risk of liver injury/failure given the lack of signal for it (Senior, page 17) nor do they think a mandatory registry is justified.

Reviewer comment:
While there is not a strong hepatotoxicity signal in either the pivotal trial or pooled data for 10 mg or less of macitentan, exposure is limited. There are cases meeting the liver test criteria for Hy's Law, but in most of these, alternative causes of elevated transaminases can be identified (mostly right heart failure, common in patient with PAH). I recommend that the hepatic findings from SERAPHIN and the potential for ERA –related hepatotoxicity be described in labeling. The sponsor should also be required to design and conduct a postmarketing registry to better characterize the hepatic safety profile once it is marketed. Periodic reporting and follow-up of liver cases of interest should also be required so that serious cases can be identified early.

8. Advisory Committee Meeting

Not applicable

9. Pediatrics

As this product has been granted Orphan Drug Status, a pediatric assessment (or waiver or deferral) under the Pediatric Research Equity Act is not required.

10. Other Relevant Regulatory Issues

None

11. Labeling

Pending (see labeling attached to action letter)

12. Recommendations/Risk Benefit Assessment

I recommend approval of macitentan to reduce the risk of PAH-related death and hospitalization from PAH (pending satisfactory results from the outstanding inspection report). I also recommend the following:

- Macitentan should be approved with a REMS with elements to assure safe use (ETASU) similar to that for ambrisentan to manage the risk of teratogenicity.
- The sponsor should be required to develop and implement a prospective registry to better characterize the hepatic safety profile of macitentan in the post-marketing setting.
- The sponsor should be required to perform enhanced pharmacovigilance to identify, follow-up, and report liver cases of interest in a timely fashion.
- The sponsor should be encouraged to develop a lower dose tablet for use in patients who require concomitant CYP 3A inhibitor therapy (i.e., ritonavir for HIV).

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/s/

MARY R SOUTHWORTH
09/19/2013