

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**204410Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION**  
**REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: October 17, 2013

Reviewer(s): Jason Bunting, PharmD  
Division of Risk Management

Team Leader: Kimberly Lehrfeld, PharmD  
Division of Risk Management

Division Director: Claudia Manzo, PharmD  
Division of Risk Management

Subject: Review evaluates the Sponsor's proposed risk evaluation  
and mitigation strategy (REMS)

Drug Name(s): Opsumit<sup>®</sup> (macitentan)

Therapeutic Class: Endothelin receptor antagonist

Dosage and Route: 10 mg, oral tablets

Application Type/Number: NDA 204-410

Submission Number: eCTD Sequence No. 0000

Applicant/sponsor: Actelion Pharmaceuticals, Ltd.

OSE RCM #: 2013-899

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## EXECUTIVE SUMMARY

DRISK has determined that a risk evaluation and mitigation strategy (REMS) is required for Opsumit<sup>®</sup> (macitentan) to ensure the benefits outweigh the risk of teratogenicity. The proposed requirements for the REMS include a Medication Guide, elements to assure safe use (ETASU) including prescriber certification, dispenser certification, and documentation of safe use conditions, an implementation system, and timetable for submission of assessments.

It was determined by the Agency that REMS for teratogenic drugs in the PAH setting should be harmonized and standardized to avoid confusion and burden on stakeholders; thus, the final REMS for Opsumit should mimic the Letairis<sup>®</sup> (ambrisentan) and Adempas<sup>®</sup> (riociguat) REMS programs.

The final proposed REMS for Opsumit was received on October 17, 2013, containing the agreed upon elements, and DRISK found it to be acceptable.

## 1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK's) assessment for the need for a Risk Evaluation and Mitigation Strategy (REMS) for Opsumit<sup>®</sup> (macitentan) oral tablets (NDA 204-410), submitted by Actelion Pharmaceuticals, Ltd on October 19, 2012.

The Sponsor included a proposed REMS in their submission. The proposed REMS is to mitigate the risk of teratogenicity and includes the following elements: Medication Guide, elements to assure safe use (ETASU) including prescriber certification, dispenser certification, and documentation of safe use conditions, an implementation system, and timetable for submission of assessments.

### 1.1 BACKGROUND

Macitentan is an endothelin receptor antagonist (ERA) that prevents the binding of endothelin (ET)-1 to its receptors ET<sub>A</sub> and ET<sub>B</sub>. The proposed indication for macitentan is the long-term treatment of pulmonary arterial hypertension (PAH, WHO Group I) in adult (b) (4)

Macitentan may be effective when used as monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids.

Macitentan is formulated as 10 mg tablets for oral administration. The recommended dose is 10 mg taken once daily, with or without food.

Currently, there are two other FDA approved ERAs for the treatment of PAH, WHO Group I, which include Tracleer<sup>®</sup> (bosentan) and Letairis<sup>®</sup> (ambrisentan). The serious risks of concern associated with Tracleer are teratogenicity and hepatotoxicity. The serious risk of concern associated with Letairis is teratogenicity. Another drug approved for use in the treatment of PAH, Adempas<sup>®</sup> (riociguat), utilizes a different mechanism of action than Letairis and Tracleer; however, it too carries a risk of teratogenicity.

Due to these risks of concern, Tracleer, Letairis, and Adempas are approved with a REMS that include a medication guide, elements to assure safe use (ETASU) including

prescriber certification, dispenser certification, and documentation of safe use conditions, an implementation system, and timetable for submission of assessments.

## 1.2 REGULATORY HISTORY

- March 15, 2012: A Type B Pre-NDA meeting was held with the Sponsor to discuss the proposed NDA for Opsumit for the treatment of PAH. Actelion proposed that a REMS to mitigate the risk of teratogenicity would be submitted with the NDA. Actelion indicated in their briefing package for the Pre-NDA meeting that the REMS they would submit would consist of a Medication Guide and timetable for submission of assessments.
- October 19, 2012: NDA submission received, which included a proposed REMS. The application was granted standard review with a goal action date of October 19, 2013.
- July 22, 2013: FDA sent interim comments (set #001) to Actelion via email.
- August 5, 2013: Actelion responded to FDA's interim comments (set #001) via email.
- September 6, 2013: FDA held a teleconference with Actelion to discuss their proposal to remove (b) (4) from the proposed REMS and replace it with a (b) (4).
- September 24, 2013: FDA sent interim comments (set #002) to Actelion via email.
- September 30, 2013: Actelion responded to FDA's interim comments (set #002) via email.
- October 4, 2013: FDA sent interim comments (set #003) to Actelion via email.
- October 8, 2013: Actelion responded to FDA's interim comments (set #003) via email.
- October 11, 2013: FDA sent the final REMS documents to sponsor, via email.
- October 17, 2013: Actelion submitted the final REMS document and appended REMS materials to their application

## 2 MATERIALS REVIEWED

### 2.1 DATA AND INFORMATION SOURCES

- Actelion Pharmaceuticals, Ltd. proposed REMS for Opsumit® (macitentan) oral tablets, NDA 204-410 (eCTD Sequence No. 0000), received October 19, 2012
  - Amendment to REMS submission, received via email August 5, 2013
  - Amendment to REMS submission, received via email September 30, 2013
  - Amendment to REMS submission, received via email October 8, 2013
  - Amendment to REMS submission, received on October 17, 2013 (eCTD Sequence No. 0019)

### 2.2 ADDITIONAL MATERIALS INFORMING THE REVIEW

- Actelion Pharmaceuticals, Ltd. Summary of Clinical Efficacy for Opsumit (macitentan), received October 19, 2012

- Actelion Pharmaceuticals, Ltd. Summary of Clinical Safety for Opsumit (macitentan), received October 19, 2012
- Actelion Pharmaceuticals, Ltd. Draft Prescribing Information for Opsumit (macitentan), received October 19, 2012
- Division of Cardiovascular and Renal Products Primary Pharmacology/Toxicology Review, Link W, June 15, 2013
- Division of Cardiovascular and Renal Products Primary Clinical Review, Gordon M, completed June 21, 2013
- Division of Risk Management Interim Comments on Opsumit Risk Evaluation and Mitigation Strategy (REMS) set #001, dated July 22, 2013
- Division of Cardiovascular and Renal Products Addendum to Primary Clinical Review regarding liver toxicity, Gordon M, completed July 25, 2013
- Office of Surveillance and Epidemiology Memorandum to Division of Cardiovascular and Renal Products regarding hepatic safety of Opsumit, Senior J, completed September 9, 2013
- Division of Risk Management Interim Comments on Opsumit Risk Evaluation and Mitigation Strategy (REMS) set #002, dated September 24, 2013
- Division of Risk Management Interim Comments on Opsumit Risk Evaluation and Mitigation Strategy (REMS) set #003, dated October 4, 2013

### **3 RESULTS OF REVIEW OF PROPOSED OPSUMIT RISK EVALUATION AND MITIGATION STRATEGY**

#### **3.1 OVERVIEW OF CLINICAL PROGRAM**

The NDA for Opsumit is supported by a single, randomized, double-blind, placebo-controlled study (AC-055-302/SERAPHIN) designed to evaluate the effect of Opsumit on morbidity and mortality in patients with symptomatic PAH. A total of 742 patients were randomized in SERAPHIN in a 1:1:1 ratio to receive macitentan 3 mg (n=250), macitentan 10 mg (n=242), or placebo (n=250). The primary efficacy endpoint in the SEARPHIN study was assessed as the time from start of study treatment to the first morbidity or mortality event up to end of treatment plus seven days (EOT + 7 days). Secondary endpoints included change in 6-minute walk distance (6MWD) from baseline to month 6, proportion of patients with improvement in modified WHO functional class from baseline to month 6, time to death due to PAH or hospitalization for PAH up to EOT + 7 days, and time to death of all causes up to EOT + 7 days.

**Key efficacy findings:** In the double-blind PAH population, a primary endpoint morbidity or mortality event was recorded for 95 patients (38%) in the macitentan 3 mg group, 76 patients (31.4%) in the macitentan 10 mg group, and 116 patients (46.4%) in the placebo group. The hazard ratio versus placebo for the occurrence of a morbidity or mortality event was 0.686 (p=0.0044) in the macitentan 3 mg group and 0.559 (p<0.0001) in the macitentan 10 mg group.

Secondary endpoints showed benefit in the macitentan groups versus placebo in the double-blind PAH population. After 6 months of treatment, the placebo group had a mean decrease in 6MWD of 9.4 m compared to a mean increase of 7.4 m and 12.5 m for the macitentan 3 mg and 10 mg groups, respectively. WHO functional class remained

relatively unchanged from baseline to month 6; however, those in the macitentan groups were more likely to have improved and less likely to have become worse. Death due to PAH or hospitalization for PAH up to EOT + 7 days was recorded for 65 patients (26%) in the macitentan 3 mg group, 50 patients (21%) in the macitentan 10 mg group, and 84 patients (34%) in the placebo group. The hazard ratio versus placebo for a death due to PAH or hospitalization for PAH up to EOT + 7 days was 0.669 (p=0.0146) in the macitentan 3 mg group and 0.500 (p<0.0001) in the macitentan 10 mg group. Death of all causes up to EOT + 7 days was recorded for 21 patients (8%) in the macitentan 3 mg group, 14 patients (6%) in the macitentan 10 mg group, and 19 patients (8%) in the placebo group. The hazard ratio versus placebo for death of all causes up to EOT + 7 days was 0.971 (p=0.9249) in the macitentan 3 mg group and 0.638 (p=0.2037) in the macitentan 10 mg group.

*Reviewer comment: The statistical analyses suggest that the efficacy of macitentan 10 mg is supported in regard to the primary and secondary endpoints while macitentan 3 mg shows little to no benefit versus placebo. Furthermore, there is a statistically significant finding of a reduction in death due to PAH or hospitalization for PAH in the macitentan 10 mg group versus placebo. There was not a statistically significant finding of death of all causes for either drug treated group.*

**Key safety findings:** In the double-blind PAH population, 95.3% of patients in the pooled macitentan group had any AE, 48.6% had any SAE, 12.2% had any AE leading to treatment discontinuation, and 7.7% died. This is compared to 96.4%, 55.0%, 12.4%, and 8.4%, respectively for placebo treated patients. The most frequently reported AE, SAE, and AE leading to treatment discontinuation for both Opsumit and placebo was PAH (i.e., worsening of PAH) and occurred more frequently in the placebo group than in the macitentan groups (see table 1).

**Table 1 - PAH AE, SAE, and AE leading to treatment discontinuation in the double-blind PAH population**

Pulmonary Arterial Hypertension	Macitentan 3mg (N=250) n (%)	Macitentan 10mg (N=242) n (%)	Total Macitentan (N=492) n (%)	Placebo (N=249) n (%)
PAH AE	75 (30.0)	53 (21.9)	128 (26.0)	87 (34.9)
PAH SAE	48 (19.2)	32 (13.2)	80 (16.3)	56 (22.5)
PAH AE leading to treatment d/c	6 (2.4)	4 (1.7)	10 (2.0)	10 (4.0)

The clinical reviewer for this NDA, Maryann Gordon, M.D., noted in her review the following important safety findings from the SERAPHIN Study:

- The incidence rates of reported deaths were similar for the 3 treatment groups: placebo (8%), macitentan 3 mg (9%), and macitentan 10 mg (7%). Most deaths were attributed to right ventricular failure or PAH.

- The adverse events reported more often in the macitentan groups compared to placebo included anemia, headache, thrombocytopenia, hypotension and various infections (URTI, nasopharyngitis, bronchitis, UTI, and others).
- Liver function test abnormalities were reported more often in the placebo group (perhaps a result of worsening PAH in the placebo group). However, the dose of macitentan was limited to 10 mg or less.
- Anemia reported as a serious adverse events was more frequent in the macitentan 3 and 10 mg groups (2% and 3%, respectively) compared to placebo (<1%). Anemia was given as the reason for drop outs in 2 patients (1 for each macitentan group).
- Of the 4 reports of serious acute or relapsing pancreatitis, all were by patients in the macitentan groups (3 and 1, macitentan 3 mg and 10 mg, respectively).

*Reviewer comment: Events associated with worsening of disease led to the overall incidence of AEs, SAEs, AEs leading to discontinuation of treatment, and death reported in the macitentan-treated groups to be slightly lower than in the placebo-treated group. Overall, the safety profile for Opsumit is similar to that of other approved ERAs and most risks may be mitigated via professional labeling.*

## **3.2 SERIOUS SAFETY CONCERNS**

### **3.2.1 Teratogenicity**

The pharmacology/toxicology reviewer for this NDA, William Link, found that serious malformations of the fetus are apparent with administration of Opsumit. In rats, treatment with Opsumit resulted in a number of craniofacial abnormalities as well as cardiovascular abnormalities and affected all fetuses. The findings were consistent with other ERA's, bosentan and ambrisentan, currently marketed and covered by a REMS to mitigate the risk of teratogenicity.

### **3.2.2 Drug-induced Liver Injury**

Because Opsumit is chemically similar to bosentan and sitaxsentan, drugs associated with drug-induced liver injury, Dr. Gordon conducted an additional review of the effects of Opsumit on the liver. According to Dr. Gordon, she "...found, at best, only a weak link between possible liver injury and the use of this agent." However, she caveated her findings by stating that the number of patients exposed to the drug is small and the majority of doses studied has been 10 mg or less, so the safety of higher doses is unknown. It was also noted that liver findings in this patient population are often confounded due to the fact that worsening PAH itself may cause liver injury secondary to right heart failure.

John Senior, M.D., Associate Director for Science, Office of Surveillance and Epidemiology was consulted to review the hepatic safety of Opsumit. While Dr. Senior concedes that the data included in this NDA does not provide a signal for liver toxicity, he remains concerned that the study size was much too small to detect such a signal and it may be years after marketing before cases of death due to liver injury emerge.

### 3.3 SPONSOR'S PROPOSED RISK EVALUATION AND MITIGATION STRATEGY

The Sponsor has proposed a REMS for Opsumit to mitigate the risk of fetal exposure in females of reproductive potential (FRP). The following describes the Sponsor's proposed REMS, submitted on October 19, 2012.

#### 3.3.1 Goals

The Sponsor's proposed goals of the Opsumit risk evaluation and mitigation strategy are:

-  (b) (4)
- 

*Reviewer comment: The goals of the Opsumit REMS should be aligned with the goals of the other comparable programs (i.e., Letairis REMS) and are as follows:*

1. *To inform prescribers, patients, and pharmacists about the serious risk of teratogenicity and safe-use conditions for Opsumit*
2. *To minimize the risk of fetal exposure and adverse fetal outcomes in females of reproductive potential (FRP) prescribed Opsumit*
  - a) *Females who are pregnant must not be prescribed Opsumit*
  - b) *Females taking Opsumit must not become pregnant*

#### 3.3.2 REMS Elements

##### 3.3.2.1 Medication Guide

The Sponsor has proposed that a Medication Guide (MG) will be dispensed with each Opsumit prescription in accordance with 21 CFR 208.24. The prescriber will attest to reviewing the MG with each patient.

*Reviewer comment: DRISK agrees that a MG should be included in the Opsumit REMS Program. The MG will be provided to all patients and as outlined below in Section 3.3.2.2.1, HCPs will review the MG with the targeted patient population.*

##### 3.3.2.2 Elements to Assure Safe Use

The Sponsor has proposed elements to assure safe use (ETASU) consisting of prescriber certification, dispenser certification, and documentation of safe use conditions.

*Reviewer comment: DRISK agrees that the Opsumit REMS Program should consist of prescriber certification, dispenser certification, and documentation of safe use conditions. These are the same requirements of other PAH drugs that have a REMS for teratogenicity.*

##### 3.3.2.2.1 Healthcare providers who prescribe Opsumit will be specially certified

To become certified, the Sponsor proposes that healthcare providers who prescribe Opsumit must agree to the following:

-  (b) (4)

- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

(b) (4)

Reviewer comment: DRISK agrees that healthcare providers who prescribe Opsumit must be specially certified. [Redacted]

(b) (4)

[Redacted] to align with the recommendations from a Drug Safety and Risk Management (DSaRM) Advisory Committee (AC) meeting, held in December 2012 regarding teratogenic drugs, the REMS should target the affected population (i.e., all females) when possible. Females should be enrolled in the REMS program according to their reproductive potential status as one of the following:

- female of reproductive potential (FRP),
- female of non-reproductive potential (FNRP), pre-pubertal, or
- female of non-reproductive potential (FNRP), post-menopausal.

Furthermore, prescribers must adhere to the requirements for each subset of female patient as described in the table below:

Requirement	Females of Reproductive Potential	Females of Non-Reproductive Potential	
		Pre-pubertal	Post-menopausal
Prescriber enrolls female patients into Opsumit REMS Program	X	X	X
Prescriber counsels with Opsumit REMS Guide for Females Who Can Get Pregnant	X		
Prescriber counsels with Opsumit Medication Guide, including the risk of teratogenicity	X	X*	
Prescriber must order and review pregnancy tests prior to initiation of treatment, monthly during treatment, and for 1 month after stopping treatment	X		
Prescriber must verify reproductive status annually in Pre-pubertal patients 8 years of age or older by completing the Opsumit REMS Reproductive Potential Status Form		X	
Prescriber must complete the Opsumit REMS Reproductive Potential Status Form upon becoming aware of any change in reproductive potential status within 10 business days of awareness	X	X	X

\*Counsel Pre-pubertal Female patient and/or parent/guardian

### 3.3.2.2.2 Opsumit will only be dispensed by pharmacies, practitioners, or health care settings that are specially certified

To become certified, the Sponsor has proposed that pharmacies, practitioners, and healthcare settings that dispense Opsumit attest to the following:

- 
- 
- 
- 

(b) (4)

*Reviewer comment: DRISK agrees that pharmacies, practitioners, or health care settings that dispense Opsumit must be certified. However, the need to further define dispenser type, by outpatient dispensing or inpatient dispensing, is necessary to ensure that the requirements for stakeholders are not overly burdensome and allow for continuity of care between the two dispensing settings.*

*The process by which inpatients will obtain Opsumit will be similar to the process for outpatients in that all prescribers must be certified, counsel patients, and ensure females of reproductive potential have a negative pregnancy test prior to initiating therapy. As described above in Section 3.3.2.2.1, all females will be enrolled in the Opsumit REMS Program albeit that the timing of enrollment varies with the setting where treatment is initiated. Any inpatient must be enrolled in the Opsumit REMS Program prior to discharge. If the inpatient pharmacy needs Opsumit for a specific inpatient prior to becoming enrolled in the REMS program, they may contact the Sponsor to obtain a 15 day supply of Opsumit while initiating enrollment. Inpatient pharmacies within healthcare settings will be enrolled via an enrollment form whereas outpatient pharmacies must contractually agree with the Sponsor.*

*Both inpatient and outpatient dispensing settings will need to adhere to specific requirements for each subset of female patient. While there are no dispensing restrictions on FNRPs who are post-menopausal, FNRPs who are pre-pubertal and FRPs will be limited to a 30 day supply of Opsumit. FRPs will only be dispensed Opsumit after confirmation that a pregnancy test was completed.*

### **3.3.2.2.3 Applicant will ensure that Opsumit will be dispensed only to patients enrolled in the REMS program with evidence or other documentation of safe-use conditions**

To document safe use, the Sponsor has proposed the registration (b) (4) in the REMS program by signing an enrollment form acknowledging that she has read the MG and patient education materials. The patient must also agree to be contacted prior to each dispensing of Opsumit to obtain confirmation that pregnancy testing was completed, to be counseled on the requirements of the REMS program and the risk of teratogenicity, and to be contacted by Actelion should a pregnancy occur while taking Opsumit.

*Reviewer comment: DRISK agrees that Opsumit should only be dispensed with evidence or other documentation of safe-use conditions; however, this should include (b) (4) all other female patients prescribed Opsumit as well.*

*The table in Section 3.3.2.2.1 describes the safe-use conditions for all female patients:*

### **3.3.2.3 Implementation System**

Actelion will maintain a database of prescribers, dispensers, and registered patients. Monitoring and auditing of certified dispensers will be conducted by the Sponsor to ensure compliance with the REMS program. The Sponsor will monitor the distribution of Opsumit to ensure that drug is only shipped to certified dispensers and they will track and review the location and amount of Opsumit dispensed to patients registered in the REMS program.

*Reviewer comment: DRISK agrees that an implementation system is necessary so that the Sponsor is able to monitor and evaluate, and work to improve implementation of dispenser certification and documentation of safe-use conditions.*

### **3.3.2.4 Timetable for Submission of Assessments**

The Sponsor has proposed that assessments of the Opsumit REMS program will be submitted at (b) (4) from the date of initial REMS approval. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Actelion will submit each assessment so that it will be received by the FDA on or before the due date.

*Reviewer comment: The Sponsor's proposed timetable for submission of assessments is not consistent with that of other REMS with ETASU, and more specifically with other REMS for PAH drugs that mitigate teratogenicity. Assessments for Opsumit should be submitted at 6 months and 1 year from the date of initial REMS approval, then annually thereafter.*

### **3.3.2.5 Opsumit REMS Assessment Plan**

The Opsumit REMS assessment plan will be consistent with that of the other PAH drugs with REMS for teratogenicity (i.e., Letairis and Adempas). The assessment plan should include the following:

**For the 6-month assessment and all subsequent REMS assessments submitted thereafter:**

1. Assessment of the dispensing of the *Medication Guide* in accordance with 21 CFR 208.24
2. Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
3. Number of dispensers and prescribers (stratified by medical specialty) certified, and patients enrolled during the current REMS assessment reporting period and during each previous REMS assessment reporting period
4. Patient demographics for the current REMS assessment reporting period and for previous REMS assessment reporting periods to include age, diagnosis, and the percentage number (%) of females of reproductive potential
5. An evaluation of any shipment holds due exclusively to the absence of pregnancy test results, which resulted in an actual treatment interruption and a summary of root cause analysis and any adverse events resulting from the treatment interruption
6. The frequency and reasons for dispensing >30 day supply to females of reproductive potential
7. Report on *Opsumit REMS Reproductive Potential Status Forms* including:
  - a. Number of *Opsumit REMS Reproductive Potential Status Forms* received
  - b. Number of status changes to a female of reproductive potential, including rationale for the change as indicated on the form and time between receipt of form and start of routine monthly pregnancy testing
  - c. Number of status changes to a female of non-reproductive potential, including rationale for the change as indicated on the form
8. Reports of critical observations identified during operational monitoring, including results of distribution data reconciliation.
9. Critical observations identified during Regulatory Compliance Audits and corrective actions taken to address any non-compliance.
10. An evaluation of inpatient pharmacies' compliance with REMS requirements for dispensing Opsumit (macitentan)
11. An analysis of all cases of pregnancy reported in association with Opsumit (macitentan) from any source (during the reporting period and cumulative) with attention to but not limited to:
  - a. The number of pregnancy exposures reported (during the reporting period and cumulative) and stratified by source of exposure report. A cumulative summary of pregnancy cases world-wide should be provided and at a minimum, include the following information:
    - i. Event identification number
    - ii. Indication for Opsumit

- iii. Birth control methods
    - iv. Root cause of contraception failure
    - v. Weeks gestation at termination if pregnancy terminated.
  - b. Follow-up of outstanding pregnancy reports from previous assessment reporting period
  - c. Root cause analysis of each reported pregnancy to determine the reason the Opsumit REMS program failed to prevent the pregnancy exposure
12. With respect to the Opsumit REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified

**For the 12-month and all subsequent REMS assessments submitted annually thereafter, the following assessment will also be included:**

1. An evaluation of patients' awareness and understanding of teratogenicity associated with Opsumit, including an evaluation of patient-reported compliance with contraceptive use and monthly pregnancy testing for females of reproductive potential
2. An evaluation of healthcare providers' awareness and understanding of:
  - a. The risk of teratogenicity associated with Opsumit (macitentan)
  - b. The need to exclude a pregnancy before initiating Opsumit (macitentan) therapy
  - c. The need for patients to consistently use reliable birth control and what the reliable methods of contraception are

#### **4 DISCUSSION**

A REMS for Opsumit is necessary to ensure the benefits of the drug outweigh the risk of teratogenicity. Non-clinical findings have shown that serious malformations of the fetus are apparent with administration of Opsumit and consist of a number of craniofacial and cardiovascular abnormalities. These non-clinical findings are similar to those seen with other approved ERAs for PAH, bosentan and ambrisentan, which have REMS targeting teratogenicity.

Recommendations from the DSaRM AC meeting held in December 2012, provided the basis for the Agency's current thinking regarding risk mitigation strategies for teratogenic drugs. The Letairis (ambrisentan) REMS was modified in August 2013, to incorporate these recommendations. After internal discussion with senior management, it was determined that the REMS for Opsumit should mimic the Letairis (ambrisentan) REMS to harmonize and standardize the risk mitigation approach for teratogens in the PAH setting. This will result in minimal confusion and burden on stakeholders.

The specific recommendations from the DSaRM AC that have been applied to the Letairis (ambrisentan) REMS and should be applied to the Opsumit REMS are:

- Enrollment of the at-risk patient population:

- The inclusion of males in REMS programs that only mitigate the risk of teratogenicity is not supported because of the limited information on the plausibility of the potential risk of teratogenicity due to seminal transfer; therefore, males will not be required to enroll in the REMS program.
- The inclusion of all females is necessary to ensure documentation of safe use conditions has been met by requiring prescribers to evaluate and document the clinical factors that lead to the selected reproductive status; therefore, all females will enroll with different requirements for each subset of female patient.
- Definitions of Reproductive Potential Status:
  - **Females of Reproductive Potential:**
    - Females of reproductive potential include girls who have entered puberty and all females who have a uterus and have not passed through menopause (as defined below). For the purposes of this REMS, puberty includes those girls who are at least Tanner Stage 3 and have not yet had a menses (premenarchal).
  - **Females of Non-Reproductive Potential:**
    - Pre-pubertal Females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential.
    - Post-menopausal Female: Females who have passed through menopause (as defined below).
  - **Definition of Menopause:**
    - Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or post-surgical from bilateral oophorectomy.

Requiring only females to enroll in the REMS program significantly reduces the burden on stakeholders. By tailoring the REMS requirements to the specific subsets of female patient's, burden on stakeholders will be further reduced by ensuring that the specific requirements are performed only when necessary (see Section 3.3.2.2.1 for REMS requirements for specific subsets of female patients).

## 5 CONCLUSION

In conclusion, a REMS for Opsumit (macitentan) is required to ensure the benefits outweigh the risk of teratogenicity. The minimally necessary elements for the Opsumit REMS include: Medication Guide, elements to assure safe use including prescriber certification, dispenser certification, and documentation of safe use, an implementation system, and timetable for submission of assessments.

The Opsumit REMS submitted by Actelion Pharmaceuticals, Ltd., on October 17, 2013, contains the appropriate REMS components and materials as agreed upon with the Agency.

## **ATTACHMENTS**

- Opsumit REMS Document
- Opsumit Patient Enrollment and Consent Form
- Opsumit REMS Guide for Females Who Can Get Pregnant
- Prescriber Guide for the Opsumit REMS Program
- Opsumit REMS Prescriber Enrollment and Agreement Form
- Opsumit REMS Reproductive Potential Status Form
- Opsumit REMS Inpatient Pharmacy Enrollment Form
- Opsumit REMS Website

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/s/  
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Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategies (REMS) Review**

Date: October 4, 2013

Reviewer(s): Jason Bunting, PharmD  
Division of Risk Management

Team Leader: Kimberly Lehrfeld, PharmD  
Division of Risk Management

Division Director: Claudia Manzo, PharmD  
Division of Risk Management

Subject: Interim comments on REMS – Set #003

Drug Name(s): Opsumit (macitentan)

Therapeutic Class: Endothelin Receptor Antagonist

Dosage and Route: 10 mg, oral tablets

Application Type/Number: NDA 204-410

Applicant/sponsor: Actelion Pharmaceuticals, Ltd.

OSE RCM #: 2013-123 & 2013-899

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## 1 INTRODUCTION

The purpose of this review is to document interim comments for the applicant's proposed Risk Evaluation and Mitigation Strategy (REMS) for the New Drug Application (NDA) 204-410 submitted by Actelion Pharmaceuticals, Ltd on October 19, 2012.

The application is currently under review in the Division of Cardiology and Renal Products (DCRP) for treatment of pulmonary arterial hypertension (PAH). The Sponsor included a proposed REMS in their submission to mitigate the risk of teratogenicity that includes the following elements: Medication Guide, prescriber certification, dispenser certification, documentation of safe use conditions, an implementation system and a timetable for submission of assessments.

## 2 REGULATORY HISTORY

July 22, 2013: Actelion was provided with DRISKs Interim Comments Set #001

August 5, 2013: Actelion responded to DRISKs Interim Comments Set #001 and provided updated REMS documents and materials to the Agency via email.

September 6, 2013: A teleconference was held with Actelion to discuss their proposal to remove (b) (4) from the proposed REMS and replace it with (b) (4)

September 24, 2013: Actelion was provided with DRISKs Interim Comments Set #002

September 30, 2013: Actelion responded to DRISKs Interim Comments Set #002 and provided updated REMS documents and materials to the Agency via email.

## 3 MATERIALS REVIEWED

### 3.1 SUBMISSIONS

- Actelion Pharmaceuticals, Ltd. proposed Opsumit REMS documents, received September 30, 2013 via email:
  - Opsumit REMS document
  - Opsumit REMS Patient Enrollment and Consent Form
  - Opsumit REMS Guide for Females Who Can Get Pregnant
  - Prescriber's Guide to the Opsumit REMS Program
  - Opsumit REMS Prescriber Enrollment and Agreement Form
  - Opsumit REMS Reproductive Potential Status Form
  - Opsumit REMS Inpatient Pharmacy Enrollment Form
  - Opsumit REMS Website

### 3.2 OTHER MATERIALS INFORMING THE REVIEW

- Division of Risk Management Interim Comments Set #001 on Risk Evaluation and Mitigation Strategy (REMS) for Opsumit, dated July 22, 2013.
- Division of Risk Management Interim Comments Set #002 on Risk Evaluation and Mitigation Strategy (REMS) for Opsumit, dated September 24, 2013.

## 4 SUMMARY OF APPLICANT'S PROPOSED REMS

Actelion agreed with the revised content of the REMS documents and materials as provided by the Agency in interim comments set #002 with the exception of minor revisions and the following described below:

### 4.1 REMS DOCUMENT

#### 4.1.1 Goals

Actelion proposed to replace (b) (4) in the REMS goals and throughout the REMS document to remain consistent with the Prescribing Information (PI).

*Reviewer comment:* (b) (4) the goals of this REMS and the terminology used should remain consistent with the other REMS for drugs used in pulmonary arterial hypertension that mitigate this risk..

#### 4.1.2 Outpatient Dispensing

Actelion proposed to remove the requirement for outpatient dispensers to:

- (b) (4)

The Sponsor's rationale is:

(b) (4)

*Reviewer comment:* It is essential that the dispenser verify the reproductive status of each female patient prior to dispensing, to be able to conform to the requirements of the REMS for the specific patient subgroups. While it is not necessary that the dispenser verify reproductive status with Actelion Pathways prior to each dispensing, it is necessary that they verify reproductive status using information provided by Actelion Pathways and stored in their database. DRISK will provide language to clarify this requirement.

#### 4.1.3 Inpatient Dispensing

Actelion proposed to allow inpatient pharmacies the ability to obtain a 15 day supply of Opsumit for a specific inpatient while the inpatient pharmacy initiates enrollment in the Opsumit REMS Program. DRISK had proposed allowing a 14 day supply, but Opsumit will be available in a 15 day blister package; therefore, allowing a 15 day supply would match the available package size.

*Reviewer comment:* The agency agrees to allow a 15 day supply.

#### 4.1.4 Timetable for Submission of Assessments

Actelion proposed to submit REMS Assessments for Opsumit to FDA at [REDACTED] (b) (4) from the date of approval as opposed to 6 months and 1 year from the date of approval, then annually thereafter. The Sponsor's rationale is:

[REDACTED] (b) (4)

*Reviewer comment: DRISKs current thinking is that assessments for drugs with ETASU, and specifically for teratogenic drugs, will be submitted at 6 months and 1 year from the date of approval of the REMS, then annually thereafter. Furthermore, DRISK does not require that the assessment report align with the International birth date or PBRER.*

### 5 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the Opsumit (macitentan) REMS proposal be sent to the applicant. Please request that the applicant respond to these comments as soon as possible to facilitate further review within the Prescription Drug User Fee Act (PDUFA) deadline for this NDA submission.

The comments below are based on DRISK's preliminary review of the REMS proposal for Opsumit (macitentan). Appended to this review are the REMS proposal and REMS documents including our track changes (see Attachments). The applicant should be reminded that the REMS Supporting Document must be consistent with all changes made to the REMS document.

### 6 COMMENTS FOR THE APPLICANT

The Agency accepts Actelion's revisions to the Opsumit REMS provided on September 30, 2013 with the exception of the following, detailed below or included in the track change documents.

#### 6.1 GLOBAL COMMENTS

For version control, we used the clean version of materials that were sent from the Sponsor as our base documents, and have provided track changes to those files.

#### 6.2 REMS DOCUMENT

See Attachment 8 for track changes.

The attached REMS document should be considered the final version of the Opsumit REMS document. No further revisions will be accepted.

##### 6.2.1 REMS Goals

We understand Actelion's rationale to replace [REDACTED] (b) (4) to remain consistent with how the risk is conveyed in the Prescribing Information. However, for the purpose of the REMS, we prefer to keep the terminology consistent with that of other REMS programs targeting teratogenicity.

## 6.2.2 Elements to Assure Safe Use

### 6.2.2.1 Outpatient Dispensing

We agree that the outpatient dispenser is capable of verifying reproductive potential status using the information provided by Actelion Pathways without an additional contact to Actelion Pathways prior to dispensing. However, we maintain that the outpatient dispenser must verify the reproductive status of female patients prior to dispensing Opsumit. This requirement has been updated for clarification in the REMS document as follows:

- Verify reproductive status of female patients with information provided by Actelion Pathways prior to each dispensing of Opsumit.

### 6.2.2.2 Inpatient Dispensing

We agree that a 15 day supply of Opsumit may be obtained from Actelion for a specific inpatient while the inpatient pharmacy initiates enrollment in the Opsumit REMS Program. This is to correspond with the available 15 day blister package of Opsumit.

Additionally, we have revised the allowed (b) (4) temporary supply of Opsumit to be dispensed to patients upon discharge from the healthcare facility to a 15 day temporary supply for the reason mentioned above.

## 6.2.3 Timetable for Submission of Assessments

Actelion's request to submit assessments at (b) (4) after initial approval of the REMS, and then annually thereafter is denied. The Agency does not require a REMS Assessment report to be aligned with the International birthdate or the PBRER reporting cut-off date. Actelion will submit assessments for Opsumit to the FDA at 6 months and 1 year from the date of the initial REMS approval, and then annually thereafter. However, patient and prescriber surveys to evaluate knowledge will not be required until the 1 year assessment.

## 6.3 INFORMATION NEEDED FOR ASSESSMENT

The revised Assessment Plan is currently under review and comments on the Assessment Plan will be provided in our next set of comments.

## 6.4 REMS MATERIALS

### 6.4.1 Opsumit REMS Patient Enrollment and Consent Form

See Attachment 1 for track changes.

Actelion proposes to remove the statement from the form:

(b) (4)

The Agency understands that the form may not be available to complete and submit on-line at time of product launch; however, it must be accessible on the Opsumit REMS website at time of product launch for viewing and printing.

#### **6.4.2 Opsumit REMS Guide for Females Who Can Get Pregnant**

See Attachment 2 for track changes.

#### **6.4.3 Prescriber Guide to the Opsumit REMS Program**

See Attachment 3 for track changes.

#### **6.4.4 Opsumit REMS Prescriber Enrollment and Agreement Form**

See Attachment 4 for track changes.

#### **6.4.5 Opsumit REMS Reproductive Potential Status Form**

See Attachment 5; no changes.

#### **6.4.6 Opsumit REMS Inpatient Pharmacy Enrollment Form**

See Attachment 6 for track changes.

#### **6.4.7 Opsumit REMS Website**

See Attachment 7 for track changes.

### **6.5 GENERAL COMMENTS**

Resubmission Requirements and Instructions: Submit the revised proposed REMS for Opsumit (macitentan) with attached materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

## **7 REMS SUPPORTING DOCUMENT**

The REMS Supporting Document must be consistent with all changes made to the REMS document and REMS materials.

### **ATTACHMENTS**

Attachment 1 - Opsumit Patient Enrollment and Consent Form

Attachment 2 - Opsumit REMS Guide for Females Who Can Get Pregnant

Attachment 3 - Prescriber Guide to the Opsumit REMS Program

Attachment 4 - Opsumit REMS Prescriber Enrollment and Agreement Form

Attachment 5 - Opsumit REMS Reproductive Potential Status Form

Attachment 6 - Opsumit REMS Inpatient Pharmacy Certification Form

Attachment 7 - Opsumit REMS Website

Attachment 8 - Opsumit REMS document

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/s/  
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JASON A BUNTING  
10/04/2013

KIMBERLY LEHRFELD  
10/08/2013

## **Risk Evaluation and Mitigation Strategy (REMS) Memorandum**

**U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
ODE-1  
Division of Cardiovascular and Renal Products**

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**NDA #:** 204410  
**Product:** Opsumit (macitentan) 10 mg tablets  
**APPLICANT:** Actelion  
**FROM:** Mary Ross Southworth, PharmD  
**DATE:** September 25, 2013

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Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Opsumit (macitentan) to ensure that the benefits of the drug outweigh the risk of teratogenicity. In reaching this determination, we considered the following:

- A. Opsumit (macitentan) will be indicated for the treatment of pulmonary arterial hypertension (PAH). The exact number of people affected with pulmonary hypertension in the United States is unknown; based on registry data prevalence rates are approximately 15 per million<sup>1</sup>.
- B. Pulmonary hypertension is associated with significant morbidity and mortality. Symptoms include decreased exercise tolerance, shortness of breath, and fatigue; symptoms often may lead to hospitalization. Disease progression eventually leads to right ventricular heart failure. The mortality rate at 1 year is approximately 15%.
- C. Opsumit (macitentan) is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group 1) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-

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<sup>1</sup> ACCF/AHA Expert Consensus Document on Pulmonary Hypertension, 2009.

minute walk distance, worsened PAH symptoms and need for additional PAH treatment). Opsumit also reduced hospitalization for PAH.

- D. Opsumit (macitentan) will be used chronically (life-long).
- E. Opsumit (macitentan) is associated with teratogenicity in animal studies. Its use is contraindicated in pregnancy. The background incidence of pregnancy in patients with PAH is unknown; however, such patients are generally discouraged from becoming pregnant because of the significant risk of maternal and neonatal morbidity and mortality.
- F. Opsumit (macitentan) is a new molecular entity.

In accordance with section 505-1 of the FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Opsumit (macitentan). FDA has determined that Opsumit (macitentan) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Opsumit (macitentan). FDA has determined that Opsumit (macitentan) is a drug for which patient labeling could help prevent serious adverse effects and that has a serious risk (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients' decisions to use, or continue to use, Opsumit (macitentan) and that the drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

The elements of the REMS will be a Medication Guide and elements to assure safe use, including:

- Healthcare providers will be certified.
- Pharmacies and other facilities that dispense Opsumit (macitentan) will be certified.
- Opsumit (macitentan) will be dispensed only with documentation of safe use conditions.

The elements of the REMS also include an implementation system and a timetable for submission of assessments of the REMS.

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/s/  
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MARY R SOUTHWORTH  
10/17/2013

**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategies (REMS) Review**

Date: September 24, 2013

Reviewer(s): Jason Bunting, PharmD  
Division of Risk Management

Team Leader: Kimberly Lehrfeld, PharmD  
Division of Risk Management

Division Director: Claudia Manzo, PharmD  
Division of Risk Management

Subject: Interim comments on REMS – Set #002

Drug Name(s): Opsumit (macitentan)

Therapeutic Class: Endothelin Receptor Antagonist

Dosage and Route: 10 mg, oral tablets

Application Type/Number: NDA 204-410

Applicant/sponsor: Actelion Pharmaceuticals, Ltd.

OSE RCM #: 2013-123 & 2013-899

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## 1 INTRODUCTION

The purpose of this review is to document interim comments for the applicant's proposed Risk Evaluation and Mitigation Strategy (REMS) for the New Drug Application (NDA) 204-410 submitted by Actelion Pharmaceuticals, Ltd on October 19, 2012.

The application is currently under review in the Division of Cardiology and Renal Products (DCRP) for treatment of pulmonary arterial hypertension (PAH). The Sponsor included a proposed REMS in their submission to mitigate the risk of teratogenicity that includes the following elements: Medication Guide, prescriber certification, dispenser certification, documentation of safe use conditions, an implementation system and a timetable for submission of assessments.

## 2 REGULATORY HISTORY

July 22, 2013: Actelion was provided with DRISKs Interim Comments Set #001

August 5, 2013: Actelion responded to DRISKs Interim Comments Set #001 and provided updated REMS documents and materials to the Agency via email.

September 6, 2013: A teleconference was held with Actelion to discuss their proposal to remove (b) (4) from the proposed REMS and replace it with (b) (4).

## 3 MATERIALS REVIEWED

### 3.1 SUBMISSIONS

- Actelion Pharmaceuticals, Ltd. proposed Opsumit REMS documents, received August 5, 2013 via email:
  - Opsumit REMS document
  - Opsumit REMS (b) (4) Form
  - Opsumit REMS Guide for Females Who Can Get Pregnant
  - Prescriber's Guide to the Opsumit REMS Program
  - Opsumit REMS Prescriber Enrollment and Agreement Form
  - Opsumit REMS Reproductive Potential Status Form
  - Opsumit REMS Website

### 3.2 OTHER MATERIALS INFORMING THE REVIEW

- Division of Risk Management Interim Comments Set #001 on Risk Evaluation and Mitigation Strategy (REMS) for Opsumit, dated July 22, 2013.

## 4 SUMMARY OF APPLICANT'S PROPOSED REMS

Actelion agreed with the revised content of the REMS documents and materials as provided by the Agency in interim comments set #001 with the exception of the following described below:

### 4.1 DEFINITIONS OF REPRODUCTIVE POTENTIAL

Actelion agreed with the definitions provided by the Agency for females of reproductive potential (FRP) and for females of non-reproductive potential (FNRP). However, they proposed to include [REDACTED] (b) (4)

Actelion's rationale was that [REDACTED] (b) (4)

*Reviewer comment: DRISK consulted with the maternal health team (MHT) to review Actelion's request [REDACTED] (b) (4)*

#### 4.2 TIMETABLE FOR SUBMISSION OF ASSESSMENTS

Actelion proposed to retain the initial proposal to provide REMS Assessments by [REDACTED] (b) (4) as opposed to 6 months and 1 year from the date of approval, then annually thereafter. Actelion's rationale is [REDACTED] (b) (4)

Actelion further proposed that the assessment report due date be [REDACTED] (b) (4)

*Reviewer comment: DRISKs current thinking is that assessments for drugs with ETASU, and specifically for teratogenic drugs, will be submitted at 6 months and 1 year from the date of approval of the REMS, then annually thereafter. Furthermore, DRISK will not require that the assessment report align with the PBRER; therefore, the report due date will remain 60 days from the cut-off date.*

#### 4.3 OPSUMIT REMS [REDACTED] (b) (4) [REDACTED] FORM

In response to FDA's request to remove all information not related to the REMS from the REMS materials, Actelion proposed to maintain the Patient Enrollment form to serve multiple purposes including: 1) a prescription to initiate therapy, 2) enrollment of females into the REMS, and 3) consent for services that assist with patient access to therapy.

Actelion argues that the simplicity and utilization of one form serving REMS related and non-REMS related purposes will:

- improve compliance with form completion since there will not be an opportunity to complete the wrong form (if multiple forms existed)
- streamline the operational process for the certified pharmacy
- allow for patient convenience, ease of tracking, and facilitation of processes associated with treatment access in a timely manner with a reduction on potential interruptions
- ensure all pertinent patient information is accessible in one form, including the prescription

*Reviewer comment: DRISK agrees that the Patient Enrollment form may be maintained to serve multiple purposes. Although not all information collected is related to the REMS, the use of one form will prevent confusion and streamline the process for all stakeholders. Furthermore, the use of one form will be consistent with other REMS programs targeting the same set of stakeholders.*

#### **4.4 OPSUMIT REMS REPRODUCTIVE POTENTIAL STATUS FORM**

Actelion agreed to create a Reproductive Potential Status Form as a tool to annually verify the reproductive potential status of pre-pubertal females and to document changes in the reproductive potential status of FRPs and FNRPs. Actelion proposed (b) (4)

[Redacted]

*Reviewer comment:* (b) (4)

[Redacted] *the REMS document states that the prescriber is the responsible party for determining the reproductive potential status of female patients; therefore, the prescriber must be responsible for signing the form.*

#### **4.5 INFORMATION NEEDED FOR ASSESSMENTS**

Actelion agreed to provide the information needed for assessments requested by the Agency with the exception of the following:

- Actelion proposed not to include the request for an evaluation on the need to promptly discontinue Opsumit therapy in the event of a pregnancy. Actelion's rationale is that the understanding and timing of discontinuation is dependent on the course of action decided between the patient and prescriber.

- (b) (4)

*Reviewer comment: The DRISK Assessment Team agreed that an evaluation on the need to discontinue Opsumit therapy in the event of a pregnancy is not necessary. However, the Assessment Team is interested in obtaining information on why pregnancy tests are missed resulting in shipment delays and in obtaining concrete evidence of treatment interruptions.*

#### **4.6** (b) (4)

Actelion proposed (b) (4)

[Redacted]

[Redacted] (b) (4)

[Redacted] (b) (4)

*Reviewer comment: We understand that there may be medication access issues with inpatients that are admitted to a facility that is not certified to dispense the medication. However, we do not feel that the [Redacted] (b) (4) proposed by Actelion is sufficient to assure safe use of the drug. DRISK believes that offering an "emergency supply" to inpatient facilities for a specific patient will alleviate the medication access issues while the facility undergoes the certification process.*

## **5 RECOMMENDATIONS FOR THE REVIEW DIVISION**

We recommend that the following comments on the Opsumit (macitentan) REMS proposal be sent to the applicant. Please request that the applicant respond to these comments as soon as possible to facilitate further review within the Prescription Drug User Fee Act (PDUFA) deadline for this NDA/BLA submission.

The comments below are based on DRISK's preliminary review of the REMS proposal for Opsumit (macitentan). Appended to this review is the REMS proposal and REMS documents including our track changes (see Attachments). The applicant should be reminded that the REMS Supporting Document must be consistent with all changes made to the REMS document.

## **6 COMMENTS FOR THE APPLICANT**

The Agency accepts Actelion's revisions to the Opsumit REMS provided on August 5, 2013 with the exception of the following, detailed below:

### **6.1 GLOBAL COMMENTS**

#### **6.1.1 Definition for Females of Non-Reproductive Potential**

[Redacted] (b) (4)

[Redacted] (b) (4)

Remove this [Redacted] (b) (4) from all REMS materials, where applicable.

### **6.2 REMS DOCUMENT**

The Opsumit REMS document has been revised to align with program requirements. See Attachment 9 for track changes. The REMS document is still under internal review. Though we don't anticipate any additional major changes, minor revisions may be made.

## **6.2.1 REMS Components**

### **6.2.1.1 Medication Guide**

The Medication Guide must be consistent with all changes made to the REMS document.

### **6.2.1.2 Elements to Assure Safe Use**

#### **6.2.1.2.1** [REDACTED] (b) (4)

[REDACTED] (b) (4)

Therefore, the request is denied.

In order to address potential patient access issues, the FDA has included a provision in the REMS document for inpatient pharmacies that cannot immediately enroll in the Opsumit REMS program to receive up to a 14 day supply of Opsumit for a specific inpatient.

Furthermore, we have revised the REMS document and materials to refer to [REDACTED] (b) (4) as Inpatient Pharmacy Certification. Separate headers for outpatient dispensing and inpatient dispensing have been added to the REMS document in Section II.B.2., to outline the separate requirements for each.

### **6.2.1.3 Timetable for Submission of Assessments**

Actelion's request to submit assessments at [REDACTED] (b) (4) after initial approval of the REMS is denied. Actelion will submit assessments for Opsumit to the FDA at 6 months and 1 year from the date of the initial REMS approval, and then annually thereafter. However, patient and prescriber surveys to evaluate knowledge will not be required until the 1 year assessment.

## **6.3 REMS MATERIALS**

### **6.3.1 Global Comments**

For version control, we used the clean version of materials that were sent from the sponsor as our base documents, and have provided track changes to those files.

As part of FDA's review, we comment on the functionality and usability of design and layout of all communication materials. Therefore, we request that you send in a formatted version of all materials, even if content is not finalized, so that we have time to review the design of the materials.

Final language in all REMS materials will reflect what is in the approved REMS document and labeling. See Attachment 9 for track changes to the REMS document and revise all REMS materials to be consistent with the REMS document.

### 6.3.2 Opsumit REMS [REDACTED] (b) (4) Form (renamed Opsumit Patient Enrollment and Consent Form)

See Attachment 1 for track changes.

In Actelion's August 5, 2013 written response, you agreed to rename the [REDACTED] (b) (4)

However, when reviewing the form submitted, it was titled Opsumit REMS [REDACTED] (b) (4) Form.

For the final version, rename the form the Opsumit Patient Enrollment and Consent Form.

Actelion may utilize this form to serve multiple purposes as described in your August 5, 2013 response.

Increase font size for data fields.

Although we can appreciate trying to put all information that must be completed on the first page, the Patient Agreement is critical information describing the risks and requirements of the REMS program. Therefore, the Patient Agreement language must be included on the front of the form.

[REDACTED] (b) (4)  
Include the following language on the form in a section with prescriber requirements:

#### For All Females

- I acknowledge that I have counseled the patient (and parent/guardian when appropriate) that Opsumit is only available through a restricted distribution program under an FDA-required REMS.
- I will evaluate the patient and agree to document any change in reproductive potential status by submitting a *Reproductive Potential Status Form* within 10 business days of becoming aware of the change.

#### For Females of Reproductive Potential

- I acknowledge that I have counseled the patient (and parent/guardian when appropriate) on the risks of Opsumit, including the risk of serious birth defects, and that I have reviewed the *Opsumit Medication Guide* and the *Opsumit REMS Program Guide for Females Who Can Get Pregnant* with the patient (and parent/guardian when appropriate).
- I will order and review pregnancy tests prior to initiation of Opsumit treatment, monthly during treatment, and for 1 month after stopping treatment in accordance with the Opsumit REMS Program.

## **For Pre-Pubertal Females**

- I acknowledge that I have counseled the patient and parent/guardian on the risks of Letairis, including the risk of serious birth defects, and that I have reviewed the *Opsumit Medication Guide* with the patient and parent/guardian.
- I will evaluate the patient's reproductive potential status, verify reproductive potential status annually for Pre-Pubertal Females who are at least 8 years of age and older, and agree to report any change in reproductive potential status on a *Reproductive Potential Status Form* within 10 business days of becoming aware of the change.

The Actelion Pathways Services Authorization language is still very technical and lengthy. We modified the language based on the plain language principles including the *Plain Language Principles and Thesaurus for Making HIPAA Privacy Notices More Readable*. A link to the Thesaurus can be found here: [http://www.nwi.pdx.edu/pdf/str-based-comm\\_hipaa-plain-lang.pdf](http://www.nwi.pdx.edu/pdf/str-based-comm_hipaa-plain-lang.pdf)

### **6.3.3 Opsumit REMS Guide for Females Who Can Get Pregnant**

See Attachment 2 for track changes.

### **6.3.4 Prescriber's Guide to the Opsumit REMS Program**

See Attachment 3 for track changes.

### **6.3.5 Opsumit Prescriber Enrollment and Agreement Form**

See Attachment 4 for track changes.

### **6.3.6 Opsumit REMS Reproductive Potential Status Form**

See Attachment 5 for track changes.

Per the REMS document, the prescriber must be the authority that signs this form.

### **6.3.7 Opsumit REMS (b) (4) Form (renamed Opsumit REMS Inpatient Pharmacy Enrollment Form)**

See Attachment 6 for track changes.

### **6.3.8 Opsumit REMS Website**

See Attachment 7 for track changes.

We have made edits to your proposed website. However, we will have additional comments when we are able to see screen shots and the layout for the website. We remind you to use bullets, white space, and fewer lines of text when possible when developing your website.

## **6.4 INFORMATION NEEDED FOR ASSESSMENT**

See Attachment 8 for track changes to the Assessment Plan.

Actelion will submit assessments for Opsumit to the FDA at 6 months and 1 year from the date of the initial REMS approval, and then annually thereafter. Survey's will not need to be submitted with the assessment at 6 months, but will be required for the assessment at 1 year from date of approval and annually thereafter. See Attachment 8 for an updated Assessment plan reflecting this requirement.

(b) (4)

However, assessments are due on or before the due date and the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Revise your assessment data collection cutoff dates and assessment due dates appropriately as describe in the REMS document.

#### **6.4.1 Evaluation of shipment holds**

We recognize that routine pharmacovigilance activities surrounding the use of Opsumit will occur, however, the adverse events referred to in this assessment plan item refer to adverse events resulting from treatment interruptions, which may not be captured through routine pharmacovigilance. In all previous REMS assessment reports in similar programs, shipment holds have been used as a surrogate for treatment interruptions. We are very interested in obtaining additional information on the reasons why FRP may miss the monthly pregnancy test, in the hopes that it may inform any access or burden issues the patient may experience. In addition, we would like to obtain concrete information on any treatment interruptions. As the Opsumit program utilizes Certified Specialty Pharmacies to distribute to outpatients, we believe this information could be obtained during the routine monthly counseling call for those FRP with holds placed on their shipment due to missing pregnancy test information. A list of potential reasons for the missed test and the potential for a pregnancy should be incorporated into the Certified Specialty Pharmacy's monthly counseling call script.

#### **6.4.2 Analysis of post-marketing cases of pregnancy**

See Attachment 8 for track changes to this Assessment item and for a sample table of a format in which to present post-marketing cases of pregnancy.

#### **6.4.3 New information provided in the most recent PSUR or PBRER regarding pregnancy**

See Attachment 8 for track changes to this Assessment item.

### **6.5 GENERAL COMMENTS**

Resubmission Requirements and Instructions: Submit the revised proposed REMS for Opsumit (macitentan) with attached materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

## **7 REMS SUPPORTING DOCUMENT**

The REMS Supporting Document must be consistent with all changes made to the REMS document and REMS materials.

### **ATTACHMENTS**

Attachment 1 - Opsumit Patient Enrollment and Consent Form

Attachment 2 - Opsumit REMS Guide for Females Who Can Get Pregnant

Attachment 3 - Prescriber's Guide to the Opsumit REMS Program

Attachment 4 - Opsumit REMS Prescriber Enrollment and Agreement Form

Attachment 5 - Opsumit REMS Reproductive Potential Status Form

Attachment 6 - Opsumit REMS Inpatient Pharmacy Certification Form

Attachment 7 - Opsumit REMS Website

Attachment 8 - Opsumit REMS Assessment Plan and Sample Pregnancy Reporting Table

Attachment 9 - Opsumit REMS document

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/s/  
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JASON A BUNTING  
09/24/2013

KIMBERLY LEHRFELD  
09/24/2013

**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategies (REMS) Review**

Date: July 22, 2013

Reviewer(s): Jason Bunting, PharmD  
Division of Risk Management

Team Leader: Kimberly Lehrfeld, PharmD  
Division of Risk Management

Division Director: Claudia Manzo, PharmD  
Division of Risk Management

Subject: Interim comments on REMS – Set #001

Drug Name(s): Opsumit (macitentan)

Therapeutic Class: Endothelin Receptor Antagonist

Dosage and Route: 10 mg, oral tablets

Application Type/Number: NDA 204-410

Applicant/sponsor: Actelion Pharmaceuticals, Ltd.

OSE RCM #: 2013-123 & 2013-899

\*\*\* This document contains proprietary and confidential information that should not be released to the public. \*\*\*

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## 1 INTRODUCTION

The purpose of this review is to document interim comments for the applicant's proposed Risk Evaluation and Mitigation Strategy (REMS) for the New Drug Application (NDA) 204-410 submitted by Actelion Pharmaceuticals, Ltd on October 19, 2012.

The application is currently under review in the Division of Cardiology and Renal Products (DCRP) for treatment of pulmonary arterial hypertension (PAH). The Sponsor included a proposed REMS in their submission to mitigate the risk of teratogenicity that includes the following elements: Medication Guide, prescriber certification, dispenser certification, documentation of safe use conditions, an implementation system and a timetable for submission of assessments.

## 2 MATERIALS REVIEWED

- Actelion Pharmaceuticals, Ltd. proposed REMS documents, NDA 204-410 (eCTD Sequence No. 0000), received October 19, 2012
  - REMS document
  - Patient Enrollment Form
  - Patient Guide
  - Prescriber Guide
  - (b) (4) Form
  - (b) (4) Form
  - REMS supporting document

## 3 SUMMARY OF APPLICANT'S PROPOSED REMS

The Sponsor has proposed a REMS for Opsumit (b) (4)  
(b) (4) The following describes the Sponsor's proposed REMS, submitted on October 19, 2012.

### 3.1 GOALS

The Sponsor's proposed goals of the Opsumit risk evaluation and mitigation strategy are:

- (b) (4)
- (b) (4)

### 3.2 REMS COMPONENTS

The Sponsor has proposed the following REMS components:

- Medication Guide (MG)
- Elements to Assure Safe Use (ETASU)
  - Prescriber certification
  - Dispenser certification
  - Documentation of safe use conditions
- Implementation System
- Timetable for Submission of Assessments

## 4 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the Opsumit (macitentan) REMS proposal be sent to the applicant. Please request that the applicant respond to these comments as soon as possible to facilitate further review within the Prescription Drug User Fee Act (PDUFA) deadline for this NDA/BLA submission.

The comments below are based on DRISK's preliminary review of the REMS proposal for Opsumit (macitentan). Appended to this review is the REMS proposal and REMS documents including our track changes (see Attachments). The applicant should be reminded that the REMS Supporting Document must be consistent with all changes made to the REMS document.

## 5 COMMENTS FOR THE APPLICANT

### 5.1 GLOBAL COMMENTS

Revise and resubmit the REMS document and REMS materials incorporating the following recommendations:

#### 5.1.1 REMS Program Name

1. The Agency's current thinking has changed regarding names for REMS programs. Using non-REMS names for REMS programs can cause confusion to healthcare providers and patients. [REDACTED] (b) (4)  
[REDACTED] to the Opsumit REMS program to be consistent with other newly approved REMS program names.
2. Refrain from using Opsumit in all capital letters throughout the REMS document and materials. The term Opsumit is used often and having it in all capitals is distracting to the reader and makes the REMS communication pieces look more promotional in nature.

#### 5.1.2 Program Terminology and Definitions

1. Revise the term, [REDACTED] (b) (4) to the currently accepted terminology; Females of Reproductive Potential (FRP). Refer to females not of childbearing potential as Females of Non-Reproductive Potential (FNRP). Revise the REMS document and relevant REMS materials to reflect these revisions.
2. Revise the definitions for FRP and FNRP throughout the relevant REMS materials as follows:

##### Females of Reproductive Potential

Females of reproductive potential include girls who have entered puberty and all women who have a uterus and have not passed through menopause (as defined below).

For the purposes of this REMS, puberty includes those girls who are at least Tanner Stage 3 and have not yet had a menses (premenarchal).

## Females of Non-Reproductive Potential

Pre-Pubertal Females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential.

Post-Menopausal Female: Females who have passed through menopause (as defined below).

## Definition of Menopause

Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or post-surgical form bilateral oophorectomy.

## **5.2 REMS DOCUMENT**

### **5.2.1 Goals**

Revise the goals of the Opsumit<sup>®</sup> REMS as follows:

The goals of the Opsumit risk evaluation and mitigation strategy are:



### **5.2.2 REMS Components**

#### **5.2.2.1 Medication Guide**

The Medication Guide must be consistent with all changes made to the REMS document.

#### **5.2.2.2 Elements to Assure Safe Use**

##### **5.2.2.2.1 Patient Enrollment**

1. The enrollment of men in the Opsumit REMS program is not required. However, to document safe use conditions, **ALL** females must be enrolled in the Opsumit REMS program to prevent misclassification errors and ensure females who have not yet undergone puberty are adequately counseled. This recommendation is consistent with the recommendation from the FDA Drug Safety and Risk Management (DSaRM) Advisory Committee meeting held in December 2012.
2. Incorporate the following enrollment requirements, for FNRP and subpopulations of FNRP, into the REMS document:
  - a. *Pre-pubertal FNRP*: This subpopulation can become a FRP at any point in their development; therefore, prescribers must (1) complete the Patient

Enrollment and Consent Form, and (2) review the contents of the Medication Guide at the time of enrollment in order to ensure this subpopulation has an adequate understanding of their potential risk for teratogenicity once they become a FRP.

- b. *Post-Menopausal FNRP*: Prescribers must complete the Patient Enrollment and Consent Form to enroll the patient. Further counseling requirements regarding the risk of teratogenicity are not required for this subpopulation.
3. The table in Attachment 1 summarizes the recommended REMS requirements for all female patients stratified by subpopulation.

#### **5.2.2.2.2 Patient Monitoring for Change in Reproductive Potential**

Implement a Reproductive Potential Status Form to ensure there is a mechanism available for prescribers to document yearly verification of a pre-pubertal FNRP or to change a female's reproductive potential status.

1. The prescriber must complete this form within 10 business days of becoming aware of a change in reproductive status for any female patient. The form should also require the prescriber to indicate the possible reason(s) for changing a female to a different category.
2. For pre-pubertal FNRP, prescribers must follow-up regularly with this subpopulation to ensure the patient begins complying with the requirements for FRP as soon as warranted. Actelion will ensure that the prescriber for each pre-pubertal FNRP who is 8 years-of-age and older verifies the female's reproductive potential status at least annually using the Reproductive Potential Status Form and begins complying with the requirements for FRP when necessary.
3. Revise the REMS document and relevant REMS materials to include a Reproductive Potential Status Form. See Attachment 3 for recommended format and content of the form.

#### **5.2.2.2.3** [REDACTED] (b) (4)

Remove the requirement [REDACTED] (b) (4) of the REMS program.

#### **5.2.2.2.4 Certified Dispensers**

Remove the following from the REMS requirements:

1. [REDACTED] (b) (4)
2. [REDACTED]

3.

(b) (4)

### 5.2.2.3 Timetable for Submission of Assessments

Actelion will submit REMS Assessments for Opsumit to the FDA at 6 months and 1 year from the date of the initial REMS approval, and then annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Actelion will submit each assessment so that it will be received by the FDA on or before the due date.

## 5.3 REMS MATERIALS

### 5.3.1 Global Comments

1. Temporary placeholder language has been included in the documents regarding the attestations of the prescriber and the agreements of the patients. Actelion must include the appropriate attestations and agreements of the patients in the materials where appropriate. Final language in REMS materials will reflect what is in the approved REMS document.
2. Formatting changes in the communication materials are inadvertent unless specifically noted in materials.
3. Make universal changes to all communication materials to reflect the modified terminology and definitions for the following:
  - Female of Reproductive Potential
  - Female of Non-Reproductive Potential
    - Pre-Pubertal Females of Non-Reproductive Potential
    - Post-Menopausal Females of Non-Reproductive Potential
4. Revise the chart describing the acceptable methods of contraception during treatment with Opsumit to match Attachment 5, Birth Control Options. We have created a concept showing four options that females of reproductive potential have when taking Opsumit. These concepts should be used in the patient and prescriber materials as appropriate, to explain the acceptable forms of birth control, replacing the current contraception charts. Actelion should use the options concept as shown, but create a user friendly design (e.g., using colors, layout, formatting) that makes the charts easy to follow and will match the look and feel of your current program materials.
5. Several of the materials describe alternate functions of PAH Pathways not related to REMS activities; remove all information not related to the REMS program (e.g., (b) (4)).

### 5.3.2 Opsumit (macitentan) Patient Enrollment Form (See Attachment 2 and Attachment 4 for suggested track changes)

1. Rename to Opsumit REMS Patient Enrollment and Agreement Form

2. Remove the first page of instructions on form.
3. Remove (b) (4) from the Prescriber Information section of the form.
4. Revise the Patient Enrollment Form to include the revised definitions for FRP and FNRP.
5. Is the Opsumit (macitentan) Patient Enrollment Form used as the original prescription hardcopy by the specialty pharmacy to fill the prescription?
  - a. If so, how does PAH Pathways, who collects the form, transmit the prescription to the specialty pharmacy?
  - b. How are subsequent prescriptions sent to the specialty pharmacy from the prescriber?
  - c. If not, why is this information requested on the enrollment form?
6. The Patient Enrollment Form contains an option to ship Opsumit to the prescriber's office. Under what circumstance, would a patient's prescription be shipped to the prescriber's office?

### **5.3.3 Getting Started with Opsumit (macitentan) (See Attachment 4 for suggested track changes)**

1. Rename to Opsumit REMS Guide for Females Who Can Get Pregnant.
2. Remove the section titled, (b) (4)
3. The section titled, *Your Steps to Treatment With Opsumit (macitentan)*, may remain in the guide, but must be revised to match the modified REMS program requirements.
4. Remove the section titled, (b) (4)

### **5.3.4 Opsumit (macitentan) Prescriber's Guide (See Attachment 4 for suggested track changes)**

1. Rename to Prescriber's Guide to the Opsumit REMS Program.
2. Remove the section titled, (b) (4) These risks are not mitigated via the REMS program.

### **5.3.5 Opsumit (macitentan) (b) (4) (See Attachment 4 for suggested track changes)**

1. Rename to Opsumit REMS Prescriber Enrollment and Agreement Form.
2. Remove (b) (4) from the Prescriber Information section of the form.

### **5.3.6 Opsumit REMS Reproductive Potential Status Form**

Use the mock Reproductive Potential Status Form (Attachment 3) as a guide to develop a data collection form for annual verification of pre-pubertal FNRP status or for changes in the reproductive potential status of FRPs or other FNRPs.

### **5.3.7 Opsumit REMS Website (See Attachment 6 for revised layout and content for the REMS website)**

1. The Agency requires a single-click, direct, prominent link off the Opsumit.com homepage to a Opsumit REMS landing page. The REMS website, [www.opsumitrems.com](http://www.opsumitrems.com), should be independent of links to the promotional and/or commercial website and non-REMS materials about the product. Do not include a link from the REMS website page back to the [www.opsumit.com](http://www.opsumit.com) website. All REMS materials should be only included on the [www.opsumitrems.com](http://www.opsumitrems.com) website.
2. How does Actelion intend to differentiate the patient population (males and females) through their REMS website? Will there be information specifically for females on that site?

## **5.4 REMS SUPPORTING DOCUMENT**

The REMS Supporting Document must be consistent with all changes made to the REMS document.

### **5.4.1 Information Needed for Assessments**

Include the following in the REMS assessments for Opsumit:

1. Assessment of the dispensing of the *Medication Guide* in accordance with 21 CFR 208.24
2. Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
3. An evaluation of patients' awareness and understanding of teratogenicity associated with Opsumit, including an evaluation of patient-reported compliance with contraceptive use and monthly pregnancy testing for FRP
4. An evaluation of healthcare providers' awareness and understanding of:
  - a. The risk of teratogenicity associated with Opsumit
  - b. The need to exclude a pregnancy before initiating Opsumit therapy
  - c. The need for patients to consistently use effective birth control and what the effective methods of contraception are

- d. The need to promptly discontinue Opsumit therapy in the event of a pregnancy
5. Number of dispensers and prescribers (stratified by medical specialty) certified, and patients enrolled during the current REMS assessment reporting period and during each previous REMS assessment reporting period
6. Patient demographics for the current REMS assessment reporting period and for previous REMS assessment reporting periods to include gender, age, diagnosis, and number (%) of FRP
7. An evaluation of any shipment holds due exclusively to the absence of pregnancy test results, which resulted in an actual treatment interruption and a summary of root cause analysis and any adverse events resulting from the treatment interruption.
8. The frequency and reasons for dispensing >30 day supply to FRP
9. Report on *Reproductive Potential Status Forms* including:
  - a. Number of *Reproductive Potential Status Forms* received
  - b. Number of status changes to a FRP, including rationale for the change as indicated on the form and time between receipt of form and start of routine monthly pregnancy testing
  - c. Number of status changes to a FNRP, including rationale for the change as indicated on the form
10. A summary of audit activities for PAH Pathways and certified pharmacies, reports of critical observations identified and the associated corrective and preventive action (CAPA) plans, and whether the CAPA plans were satisfactorily completed
11. An analysis of the post-marketing cases of pregnancy reported in association with Opsumit (during the reporting period and cumulative) with attention to but not limited to:
  - a. The number of pregnancy exposures\* reported (during the reporting period and cumulative) and stratified by source (spontaneous report, reported via PAH Pathways, enrolled in the pregnancy registry), age, and other demographics.
  - b. The pregnancy outcome for each exposed pregnancy reported (during the reporting period and cumulative).
  - c. Follow-up of outstanding pregnancy reports from previous assessment reporting period;
  - d. Root cause analysis of each reported pregnancy to determine the reason the Opsumit REMS program failed to prevent the pregnancy exposure; and

- e. Discussion of any new information provided in the most recent Periodic Safety Update Report (PSUR) or Periodic Benefit Risk Evaluation Report (PBRER) regarding pregnancy. In the electronic REMS assessment submission, include a hyperlink to the most recent PSUR/PBRER that provides information on worldwide pregnancies.

\*All pregnancy exposures reported to the sponsors from any source should be reported and analyzed as part of the REMS assessment. Pregnancy exposures will be recorded within the Opsumit REMS database as well as the global safety database, with appropriate linkage to allow matching of the cases reported in the Opsumit REMS database to cases in the global safety database.

- 12. With respect to Opsumit REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goal or whether the goal or such elements should be modified

## 5.5 GENERAL COMMENTS

Resubmission Requirements and Instructions: Submit the revised proposed REMS for Opsumit (macitentan) with attached materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the REMS document and attached materials be in separate MS Word documents. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible as individual MS Word documents.

## 6 ATTACHMENTS

- Attachment 1 Recommended REMS Requirements for All Female Patients
- Attachment 2 Opsumit REMS Patient Enrollment Form
- Attachment 3 Opsumit REMS Reproductive Potential Status Form
- Attachment 4 Opsumit REMS Forms and Guides (redlined versions)
- Attachment 5 Birth Control Options
- Attachment 6 Opsumit REMS Website

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