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OPSUMIT[®] (macitentan) Endothelin Receptor Antagonist

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Risk Evaluation and Mitigation Strategy (REMS)

I. GOALS:

The goals of the REMS are:

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

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide will be dispensed with each Opsumit prescription in accordance with 21 CFR 208.24.

The Opsumit Medication Guide is part of the REMS and is appended.

B. Elements to Assure Safe Use

1. **Healthcare providers (HCPs) who prescribe Opsumit will be specially certified.**
 - a. Actelion will ensure that HCPs who prescribe Opsumit are specially certified. Actelion will ensure that to become certified, each healthcare provider who prescribes Opsumit agrees on the *Opsumit REMS Prescriber Enrollment and Agreement Form* to:

- i. Read the Opsumit Prescribing Information (PI), the Opsumit Medication Guide, and the *Prescriber and Pharmacy Guide for the Opsumit REMS Program*
- ii. Enroll all females in the Opsumit REMS Program by completing the *Opsumit Patient Enrollment and Consent Form*
- iii. Advise all females that Opsumit is only available through a restricted distribution program called the Opsumit REMS Program
- iv. Determine whether each female is of reproductive potential as defined in the *Prescriber and Pharmacy Guide for the Opsumit REMS Program*
- v. For FRP (as defined in the *Prescriber and Pharmacy Guide for the Opsumit REMS Program*) patients:
 - 1) Review the Opsumit Medication Guide and the *Opsumit REMS Guide for Females Who Can Get Pregnant* with the patient prior to initiating treatment
 - 2) Counsel patients about the risk of teratogenicity and the need to use reliable contraception as defined in the *Prescriber and Pharmacy Guide for the Opsumit REMS Program* during Opsumit treatment and for one month following treatment discontinuation, and her medical options in the event of unprotected sexual intercourse or known or suspected contraception failure
 - 3) Order and review pregnancy tests prior to initiation of Opsumit treatment, monthly during treatment, and for one month following treatment discontinuation
 - 4) Counsel the patient if the patient fails to comply with required testing or if she is not using reliable contraception
 - 5) Counsel the patient to immediately contact her healthcare provider if she misses a menstrual period or suspects that she is pregnant
 - 6) Report a change or misclassification in reproductive status by completing the Opsumit REMS *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within ten (10) business days of becoming aware of the change
- vi. For females of non-reproductive potential (FNRP) (as defined in the *Prescriber and Pharmacy Guide for the Opsumit REMS Program*) patients:
 - 1) Pre-pubertal patients:
 - a) Review the Medication Guide with the patient and/or a parent/guardian
 - b) Counsel the patient and/or a parent/guardian about the risk of teratogenicity.

- c) Counsel the patient and/or a parent/guardian to immediately contact her healthcare provider if the patient begins to menstruate
 - d) Evaluate patients age 8 and older at least annually for any change in reproductive status and complete the *Opsumit REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* verifying their reproductive potential status
 - e) Report a change or misclassification in reproductive status by completing the *Opsumit REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within ten (10) business days of becoming aware of the change
- 2) Post-menopausal patients:
- a) Report a change or misclassification in reproductive status by completing the *Opsumit REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within ten (10) business days of becoming aware of the change
- 3) Females with other medical reasons for permanent, irreversible infertility (as defined in the *Prescriber and Pharmacy Guide for the Opsumit REMS Program*):
- a) Report any change or misclassification in reproductive status by completing the *Opsumit REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change
- vii. Report any pregnancy during Opsumit treatment to Actelion with all available information
- b. Actelion will:
- i. Ensure prescribers' certification information is linked to their enrolled patients' information in a validated secure database.
 - ii. For all females, ensure that patient information from a new prescriber is linked in a validated secure database with certification information from the prior prescriber.
 - iii. Maintain a validated secure database of all certified prescribers in the Opsumit REMS program. Actelion will ensure that the prescribers' certification requirements are met and may de-certify non-compliant prescribers until the requirements are met.
 - iv. Ensure all materials listed in or appended to the Opsumit REMS Program will be available through the Opsumit REMS Program Website (www.OpsumitREMS.com) or by calling *Actelion Pathways*[®] at 1-866-228-3546 within 60 days of modification approval.
- c. The following are part of the REMS and are appended:
- i. *Opsumit Patient Enrollment and Consent Form*

- ii. *Opsumit Patient Enrollment and Consent Form - for VA use only*
- iii. *Opsumit REMS Guide for Females Who Can Get Pregnant*
- iv. *Prescriber and Pharmacy Guide for the Opsumit REMS Program*
- v. *Opsumit REMS Prescriber Enrollment and Agreement Form*
- vi. *Opsumit REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*
- vii. *Opsumit REMS Website*

2. Pharmacies that dispense Opsumit will be specially certified

Outpatient Dispensing

- a. Actelion will ensure that pharmacies that dispense Opsumit are specially certified. Actelion will ensure that to be certified, pharmacies that dispense Opsumit have an authorized representative who is trained on the Opsumit REMS program and who attests that they will:
 - i. Train all dispensing staff on the Opsumit REMS Program procedures and REMS materials prior to dispensing Opsumit
 - ii. Put processes and procedures in place to ensure the following REMS requirements are met
 - a) Receive and accept the Opsumit Patient Enrollment and Consent Form only from *Actelion Pathways*
 - b) Dispense Opsumit only to patients who have a prescription written by a prescriber enrolled in the Opsumit REMS Program
 - c) Dispense Opsumit to females only if they are enrolled in the Opsumit REMS program
 - d) Dispense only up to a 30-day supply of Opsumit to FRP
 - e) Verify reproductive status of females with information provided by *Actelion Pathways* prior to each dispensing of Opsumit
 - f) Not transfer Opsumit to any pharmacy, practitioner or healthcare setting not certified by *Actelion Pathways*
 - g) For FRP patients:
 - 1) Counsel patients on the risk of serious birth defects and the need to use reliable contraception, as defined in the *Prescriber and Pharmacy Guide for the Opsumit REMS Program*, during Opsumit treatment and for one month after treatment discontinuation
 - 2) Inform patients of the need to complete a monthly pregnancy test and to inform their prescriber immediately if they suspect they are pregnant
 - 3) Dispense drug only upon completing the following process:
 - a) Obtain confirmation from the patient that pregnancy testing was completed
 - b) If unable to obtain confirmation that pregnancy testing was completed, or if the patient cannot be reached, obtain confirmation from the prescriber
 - c) If unable to obtain confirmation from the prescriber that pregnancy testing was completed, the certified pharmacy will:

- (i) Remind the prescriber of his/her obligation to order and review monthly pregnancy tests
 - (ii) Ask prescriber whether or not he/she authorizes the refill of Opsumit. The patient is eligible to receive a 30-day supply of Opsumit only if the prescriber authorizes the refill
- iii. Notify Actelion of any reports of pregnancy and provide all available information
- iv. Agree that the certified pharmacy may be audited by the FDA, Actelion, or a third party designated by Actelion
- b. Actelion will ensure that *Actelion Pathways* notifies certified pharmacies of a patient's change or misclassification in reproductive status within one business day of receipt of a completed *Opsumit REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*.

Inpatient Dispensing

- a. Actelion will ensure that only inpatient pharmacies (including, but not limited to, inpatient pharmacies in hospitals, long-term care facilities, prisons, and state psychiatric units) that are certified in the Opsumit REMS Program may stock Opsumit for patients being treated in the inpatient setting. In order for an inpatient pharmacy to become certified in the Opsumit REMS Program, an authorized representative must complete and submit an *Opsumit REMS Inpatient Pharmacy Enrollment Form*, agreeing to:
 - i. Complete training in the Opsumit REMS Program by reading the Opsumit Prescribing Information, Medication Guide and the *Prescriber and Pharmacy Guide for the Opsumit REMS Program*.
 - ii. Train all dispensing staff on the Opsumit REMS Program requirements and Opsumit REMS materials before they dispense Opsumit
 - iii. Put processes and procedures in place to ensure the REMS requirements are met
 - a) Dispense Opsumit only to patients under the supervision and care of a healthcare provider who is enrolled in the Opsumit REMS program
 - b) Dispense Opsumit to a female only after she has been enrolled in the Opsumit REMS program or if she will be enrolled prior to discharge from the healthcare facility. A female who has not been enrolled by the certified prescriber will not have access to Opsumit in the outpatient setting until such time that registration has been completed
 - c) Dispense no more than a 15 day temporary supply of Opsumit, to any patient, upon discharge from the healthcare facility
 - d) Not transfer Opsumit to any pharmacy, practitioner or healthcare setting not certified by *Actelion Pathways*

- iv. Audits by the FDA, Actelion or third party designated by Actelion
 - v. Notify Actelion of any reports of pregnancy during Opsumit treatment and provide all available treatment information
 - vi. Develop a process to track compliance with the conditions above and provide information about compliance to Actelion upon request
- b. Actelion will ensure that if an inpatient pharmacy needs Opsumit for a specific inpatient and is not enrolled in the Opsumit REMS Program, the inpatient pharmacy can contact *Actelion Pathways* for assistance in obtaining up to a 15 day supply of Opsumit for a specific inpatient while initiating enrollment.
- c. The following materials are part of the REMS and are appended:
- i. *Opsumit REMS Inpatient Pharmacy Enrollment Form*
 - ii. *Prescriber and Pharmacy Guide for the Opsumit REMS Program*
- 3. Opsumit will be dispensed to females with evidence or other documentation of safe use conditions**
- a. Actelion will ensure that to become enrolled, or when changing prescribers, each female signs the *Opsumit Patient Enrollment and Consent Form*.
 - b. In order to become enrolled by completing the *Opsumit Patient Enrollment and Consent Form*, FRPs must agree:
 - i. To read the Opsumit Medication Guide and the *Opsumit REMS Guide for Females Who Can Get Pregnant*
 - ii. To have a pregnancy test prior to initiation of treatment with Opsumit, monthly during Opsumit treatment, and for one month after stopping Opsumit
 - iii. To be counseled each month by the pharmacy on the need to use reliable contraception during Opsumit treatment and for one month after stopping Opsumit treatment
 - iv. To be contacted prior to each dispensing of Opsumit to obtain confirmation that pregnancy testing was completed
 - v. To be counseled on the requirements of the Opsumit REMS program and the risk of serious birth defects
 - vi. To immediately notify her healthcare provider if she misses a menstrual period or suspects that she is pregnant
 - vii. To be contacted by Actelion if she becomes pregnant while on Opsumit or within one month after treatment discontinuation

C. Implementation System

The Implementation System will include the following:

1. Actelion will maintain a validated secure database of certified dispensers and patients enrolled in the Opsumit REMS Program to monitor and evaluate implementation of the elements under Section B.2. and B.3. above.
2. Actelion will monitor the distribution of Opsumit to ensure that the drug is only shipped to certified dispensers.
3. Actelion will track Opsumit dispensing and review the amount of medication dispensed to individual patients enrolled in the Opsumit REMS Program.
4. Actelion will audit all certified outpatient pharmacies and distributors within 180 days after they are certified in the Opsumit REMS Program to ensure the Opsumit REMS Program is implemented as directed. *Actelion Pathways* will also be audited. Thereafter, Actelion will include the certified outpatient pharmacies, all distributors and *Actelion Pathways* in the company's annual audit plan. At least 10% of certified inpatient pharmacies that have ordered Opsumit will be audited each year. Corrective actions will be instituted if noncompliance is found.
5. Actelion will maintain *Actelion Pathways* to support patients, prescribers, certified pharmacies, and distributors in interfacing with the Opsumit REMS Program.
6. Actelion will ensure that all materials listed in or appended to the Opsumit REMS Program will be available through the Opsumit REMS Program Website (www.OpsumitREMS.com) or by calling *Actelion Pathways* at 1-866-228-3546.
7. Actelion will monitor and evaluate implementation of elements provided under Section B.2. and B.3. above and if needed, take steps to improve implementation of these elements.
8. Actelion will monitor certified inpatient and outpatient dispensers to ensure compliance with the Opsumit REMS Program and institute corrective actions if they are non-compliant.

D. 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.