Prescriber Guide for the Opsumit® REMS Program

(Risk Evaluation and Mitigation Strategy)
Introduction to Opsumit® (macitentan)

Indication

Opsumit® is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). Opsumit also reduced hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients were treated with Opsumit monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).
Risk of teratogenicity

Opsumit is contraindicated in females who are pregnant. Opsumit may cause fetal harm when administered to a pregnant woman. Opsumit was consistently shown to have teratogenic effects when administered to animals. If Opsumit is used during pregnancy, apprise the patient of the potential hazard to a fetus. To prevent pregnancy, females of reproductive potential must use reliable contraception during treatment and for one month after stopping Opsumit. Patients must not become pregnant while taking Opsumit.

Opsumit REMS (Risk Evaluation and Mitigation Strategy) Program

Due to the risk of teratogenicity, Opsumit is only available to females through a restricted distribution program required by the FDA called the Opsumit REMS (Risk Evaluation and Mitigation Strategy) Program.

The purpose of the Opsumit REMS Program is to:

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

Opsumit REMS Program overview

• All healthcare providers must enroll in the Opsumit REMS Program and comply with the requirements to prescribe Opsumit
• All female patients must enroll in the Opsumit REMS Program to receive Opsumit
• Prescribers must counsel Females of Reproductive Potential and Pre-pubertal Females of Non-Reproductive Potential about the risks of Opsumit, including the risk of serious birth defects.
• Prescribers must order and review pregnancy testing for Females of Reproductive Potential prior to initiation of treatment, monthly during treatment, and one month after stopping treatment.
• Report any change in a female’s reproductive potential status to the Opsumit REMS Program.
• 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 form bilateral oophorectomy.

• For Females of Reproductive Potential:
  - Pregnancy must be ruled out prior to drug initiation and monthly during treatment.
  - She must agree to be counseled on the requirements of the Opsumit REMS Program and the risks of Opsumit.
  - She must agree to be contacted by Actelion Pathways™ if she becomes pregnant either while on Opsumit or within one month of treatment discontinuation.

• Only pharmacies certified in the Opsumit REMS Program can dispense Opsumit to outpatients.

• Only inpatient pharmacies that are certified in the Opsumit REMS Program will stock Opsumit for inpatient use.
Summary of Opsumit REMS Program requirements for female patients

All prescribers must be enrolled in the Opsumit REMS Program. To become enrolled, a healthcare provider must complete and submit an *Opsumit REMS Prescriber Enrollment and Agreement Form* to the Opsumit REMS Program agreeing to follow the Opsumit REMS Program requirements.

All females must be enrolled in the Opsumit REMS Program in order to receive Opsumit. To become enrolled a patient must complete an *Opsumit Patient Enrollment and Consent Form* with her prescriber. This form must be submitted to the Opsumit REMS Program.

Prescribers must determine and document on the *Opsumit Patient Enrollment and Consent Form* whether the patient is a Female of Reproductive Potential, or a Female of Non-Reproductive Potential (Pre-pubertal Female or Post-menopausal Female). **This category must be documented on the Opsumit Patient Enrollment and Consent Form.** (See definitions of Reproductive Potential Status.)

Based on whether the patient is a Female of Reproductive Potential, a Pre-pubertal Female, or a Female of Non-Reproductive Potential, the prescriber must perform certain actions before initiating treatment, during treatment, and after the patient stops taking Opsumit.
### Summary of Opsumit® REMS Program requirements for female patients (continued)

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

*Counsel Pre-pubertal Female patient and/or parent/guardian.*
Your role in the Opsumit REMS Program

Healthcare providers must complete the following steps in the Opsumit REMS Program:

1. **Read** the Opsumit Prescribing Information and this guide to understand the risks of Opsumit and to learn about the Opsumit REMS Program

2. **Complete** an *Opsumit REMS Prescriber Enrollment and Agreement Form*

3. **Enroll** female patients into the Opsumit REMS Program by completing an *Opsumit Patient Enrollment and Consent Form*

4. **Determine** the reproductive potential of female patients

5. **Check** patient’s pregnancy status (if patient is a Female of Reproductive Potential)

6. **Educate and counsel** female patients about the risks of Opsumit

7. **Monitor** female patients’ reproductive potential status throughout treatment

The next section provides specific information on each step

1. **Read** the Opsumit Prescribing Information and this guide to understand the risks of Opsumit and to learn about the Opsumit REMS Program
   - Prescribers must understand the risks of Opsumit and become familiar with the Opsumit REMS Program

2. **Complete** an *Opsumit REMS Prescriber Enrollment and Agreement Form*
   - You will attest to understanding the risks of Opsumit and agree to comply with the Opsumit REMS Program

3. **Enroll** female patients into the Opsumit REMS Program by completing *Opsumit Patient Enrollment and Consent Form*
   - Confirm patient has agreed to comply with program requirements and has signed the form where indicated
   - Fax the completed form, along with all patient insurance information, including prescription drug benefits and medical benefits, to Actelion Pathways™ at 1-866-279-0669. Actelion Pathways administers the Opsumit REMS Program
   - Keep the original form with patient’s records

Please see accompanying full Prescribing Information, including BOXED WARNING for teratogenicity.

Reference ID: 3392795
4. **Determine the reproductive potential for female patients**

   - Prescribers should identify female patients (captured on the *Opsumit Patient Enrollment and Consent Form*) as belonging to one of the following categories:
     - Female of Reproductive Potential (FRP)
     
     or
    
     - Female of Non-Reproductive Potential (FNRP) (choose one of the options below)
       - Pre-pubertal Female of Non-Reproductive Potential
       - Post-menopausal Female of Non-Reproductive Potential

   Definitions are provided in the section “*Opsumit REMS Program Overview.*”

5. **Check patients’ pregnancy status (for Females of Reproductive Potential)**

   - Order and review pregnancy tests for the patient:
     1. Prior to initiating treatment
     2. Monthly during treatment
     3. One month after stopping treatment

   Patient must agree to be contacted prior to each shipment to confirm that a pregnancy test has been completed. She must also agree to be contacted by Actelion if she becomes pregnant while on Opsumit or within 30 days of treatment discontinuation.

6. **Educate and counsel female patients about the risks of Opsumit**

   - For all females, prescribers must:
     - Advise the patient that Opsumit is only available through a restricted distribution program called the Opsumit REMS Program.
     - Educate and counsel patients about the risks of Opsumit.

   - For FRPs, prescribers must:
     - Educate her about the risk of teratogenicity; the need to use reliable contraception during Opsumit treatment and for one month following treatment discontinuation; and her need to consider medical options in the event of unprotected sexual intercourse or known or suspected contraception failure.
– Advise the patient of the requirement for initial and monthly pregnancy tests to confirm they are not pregnant, so they can begin and continue to receive Opsumit.

– Provide ongoing counseling on the importance of using reliable contraception during Opsumit treatment and for one month after stopping treatment.

– Counsel her to immediately contact her healthcare provider if she misses a menstrual period or suspects she is pregnant.

• For FNRPs, prescribers must:
  – Provide the Opsumit Medication Guide to each Post-menopausal Female and instruct her to read it.

• For Pre-pubertal Females, prescribers must:
  – Review with her and her parent/guardian the Opsumit Medication Guide.
  – Educate her and her parent/guardian about the risk of serious birth defects.
  – Counsel her and her parent/guardian to immediately contact her healthcare provider if she gets her menstrual period.

• Prescribers must counsel any patient who fails to comply with the program requirements.

7. **Monitor patients throughout treatment**

• For FRPs, prescribers must:
  – Order and review pregnancy tests monthly during treatment with Opsumit and for one month after stopping treatment.
  – Notify the patient and Actelion if a patient’s pregnancy test is positive.

• For FNRPs, prescribers must:
  – Monitor patients for changes in reproductive status during treatment with Opsumit.
  – Report any changes in reproductive status to the Opsumit REMS Program by completing and submitting the *Opsumit REMS Reproductive Potential Status Form* within 10 business days of becoming aware of the change.
  – Verify and report the reproductive status annually for each Pre-pubertal Female who is at least 8 years of age and older by completing and submitting the *Opsumit REMS Reproductive Potential Status Form*.
Contraception options for FRPs

All FRPs must use reliable contraception during Opsumit treatment and for one month after stopping treatment. They should also have contraceptive counseling with either the prescriber or another designated healthcare provider trained in contraceptive counseling. Please refer to the table below for a complete list of acceptable contraceptive methods. A similar table can be found in the Opsumit REMS Guide for Females Who Can Get Pregnant and should be used to discuss acceptable birth control options with patients. The patient should be instructed to select one of the options listed below.

Contraceptive Options for Females of Reproductive Potential

Acceptable birth control options

<table>
<thead>
<tr>
<th>Option 1</th>
<th>Option 2</th>
<th>Option 3</th>
<th>Option 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>One method from this list:</td>
<td>One method from this list:</td>
<td>One method from this list:</td>
<td>One method from this list:</td>
</tr>
<tr>
<td>Standard intrauterine device (Copper T 380A IUD)</td>
<td>Estrogen and progesterone oral contraceptives (&quot;the pill&quot;)</td>
<td>Diaphragm with spermicide</td>
<td>Partner's vasectomy</td>
</tr>
<tr>
<td>Intrauterine system (LNg 20 IUS; progesterone IUS)</td>
<td>Estrogen and progesterone transdermal patch</td>
<td>Cervical cap with spermicide</td>
<td>PLUS One method from this list:</td>
</tr>
<tr>
<td>Progesterone implant</td>
<td>Vaginal ring</td>
<td>Progesterone injection</td>
<td>Male condom</td>
</tr>
<tr>
<td>Tubal sterilization</td>
<td>Progesterone injection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PLUS One method from this list:

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male condom</td>
<td></td>
</tr>
<tr>
<td>Diaphragm with spermicide</td>
<td></td>
</tr>
<tr>
<td>Cervical cap with spermicide</td>
<td></td>
</tr>
</tbody>
</table>
• Educate and counsel females of reproductive potential about medical options in the event of unprotected sex or known or suspected contraceptive failure

• Remind patients to report any delay in getting a period or any other reason of suspected pregnancy during treatment to you immediately

• If pregnancy is suspected for any reason, a pregnancy test must be performed

• The prescriber must notify Actelion at 1-866-228-3546 of any pregnancies that occur during treatment or within 1 month of discontinuation
Certified pharmacies

Due to the risk of serious birth defects, Opsumit is only available via a network of certified pharmacies. For a list of certified pharmacies please call Actelion at 1-866-228-3546.

Actelion Pathways™. Actelion Pathways is Actelion’s services and support program that administers the Opsumit REMS Program.

OUTPATIENT PHARMACY CERTIFICATION:

Only a limited number of certified pharmacies will dispense Opsumit for outpatients. Prior to dispensing Opsumit to any female, the pharmacy will confirm that the female and the prescriber who wrote the prescription are enrolled in the Opsumit REMS Program. If either the female or prescriber is not enrolled, Opsumit will not be dispensed.

Females of Reproductive Potential and Pre-pubertal Females will only be able to get a 30-day supply of Opsumit at one time. The Opsumit Medication Guide will be provided to all patients each time Opsumit is dispensed.

Females of Reproductive Potential will be contacted each month by the pharmacy to arrange her dispensing of Opsumit. The pharmacy will:

• Ask if she has had a pregnancy test within the last month
• Counsel her on the need to use reliable contraception during Opsumit treatment and for one month after stopping treatment
• Counsel her to inform her prescriber immediately if she misses a menstrual period or suspects that she may be pregnant, or if her reproductive status changes

For Pre-pubertal Females, pharmacies will:

• Counsel her to inform her prescriber immediately if her reproductive status changes

INPATIENT PHARMACY CERTIFICATION:

Inpatient pharmacies must agree to follow the REMS requirements, including:

• Establish systems, order sets, protocols or other measures to ensure the Opsumit REMS Program requirements are met
• Dispense only to those patients under the supervision and care of a healthcare provider who is enrolled in the Opsumit REMS Program
• Dispense to a female patient only after she has been enrolled in the Opsumit REMS Program or if she will be enrolled prior to discharge from this 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. Dispense no more than a fifteen (15) day temporary supply of Opsumit upon discharge of any patient.
• Notify Actelion Pharmaceuticals US, Inc. (“Actelion”) or FDA if any patient becomes pregnant during Opsumit treatment

• Not transfer Opsumit to any pharmacy, practitioner, or any healthcare setting not certified by Actelion Pathways

• Develop a process to track compliance with the conditions above and provide information about its compliance to Actelion

If an inpatient pharmacy needs Opsumit and is not enrolled in the Opsumit REMS Program, the inpatient pharmacy can contact the Opsumit REMS Program at 1-866-228-3546 for assistance in obtaining a 15-day supply of Opsumit for a specific inpatient while initiating enrollment.

To be certified in the Opsumit REMS Program, an authorized representative of the inpatient pharmacy must:

• Agree to follow the REMS requirements by completing and submitting an Opsumit REMS Inpatient Pharmacy Enrollment Form to the Opsumit REMS Program

  – Authorized representatives can complete the Opsumit REMS Inpatient Pharmacy Enrollment Form:

    - By fax at 1-866-279-0669
    - By calling the Opsumit REMS Program at 1-866-228-3546

• Agree that this pharmacy may be audited by the FDA, Actelion, or a designated third-party


If you have questions about Opsumit REMS Program enrollment, or if you would like more information about Opsumit, you can reach Actelion Pathways by calling toll-free at 1-866-ACTELION (1-866-228-3546).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.
The Osumit REMS Program is administered by Actelion Pathways™.

You can reach Actelion Pathways by calling toll free 1-866-ACTELION (1-866-228-3546).

For more information about the Osumit REMS Program, please visit OsumitREMS.com

Please see accompanying full Prescribing Information, including BOXED WARNING for teratogenicity.