Opsumit® (riociguat) is an endothelial receptor antagonist (ERA) 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 defined as an increase in WHO functional class II–IV symptoms treated for an average of 2 years. Patients were treated with Opsumit monotherapy or in combination with phosphodiesterase-5 inhibitors or intravenous prostacyclins. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (10%).
Prescriber Roles & Responsibilities

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

1. Read the Opsumit Prescribing Information and the Prescriber Guide for the Opsumit REMS Program 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 Enrolment and Agreement Form.

   - You will attest to understanding the risks of Opsumit and agree to comply with the Opsumit REMS Program. You can download the Opsumit REMS Prescriber Enrolment and Agreement Form here and fax it to Actelion Pathways at 1-866-279-0666. Actelion Pathways administers the Opsumit REMS Program.

3. Refer female patients into the Opsumit REMS Program by completing the Opsumit Patient Enrolment Form and Consent Form.

   - Confirm patient has agreed to comply with program requirements and has signed the form where instructed.
   - Fax the completed form to Actelion Pathways at 1-800-279-0669. Actelion Pathways administers the Opsumit REMS Program.
   - Keep the original form with patient’s records.

4. Determine the reproductive potential for female patients.

   - Prescribers should identify female patients (captured on the Opsumit Patient Enrolment Form and Consent Form) as one of the following categories:
     1. Female of Reproductive Potential
     2. Female of Non-Reproductive Potential (chose one of the options below)
     3. Postmenopausal Female of Non-Reproductive Potential

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

5. Check patients’ pregnancy status for females of Reproductive Potential.

   - Order and review pregnancy tests for the patient:
     3. One (1) month after stopping treatment.

   Patient must agree to be contacted prior to each shipment to confirm that a pregnancy test was completed. She must also agree to be contacted by Actelion if the becomes pregnant while on Opsumit or within one month of treatment discontinuation.

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

   - For all females, prescribers must:
     1. Advise the patient that Opsumit is only available through a restricted distribution program called the Opsumit REMS Program.
     2. Educate and counsel patients about the risks of Opsumit.
     4. Educate her about:
        1. The risks of serious birth defects.
        2. The need to use reliable contraception during Opsumit treatment and for one month following treatment discontinuation.
        3. Her need to consider medical options in the event of unplanned sexual intercourse or known or suspected contraception failure.
        4. 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.
        5. The importance of using reliable contraception during Opsumit treatment and for one month after stopping treatment.
        6. Counsel her to immediately contact her healthcare provider if she notices a menstrual period or suspects she is pregnant.
     7. For females of Reproductive Potential, prescribers must:
        1. Provide the Opsumit Medication Guide to each postmenopausal female and instruct her to read it.
        2. For pre-pubertal females, prescribers must:
           1. Review the guide with her and her parent/guardian.

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


   - For females of Reproductive Potential, prescribers must:
     1. Order and receive pregnancy tests monthly during treatment with Opsumit and for one month after stopping treatment.
     2. Notify the patient and Actelion if a patient’s pregnancy test is positive.
   - For females of Non-Reproductive Potential, prescribers must:
     1. Monitor patients for changes in reproductive status during treatment with Opsumit.

   - Report any changes in reproductive status to the Opsumit REMS Program within 10 business days of becoming aware of the change.
   - Follow 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.

Reporting to Actelion.

To report any pregnancies and suspected adverse reactions, contact Actelion at 1-866-228-3545.

Reporting to FDA MedWatch:

Visit www.fda.gov/medwatch or call 1-800-332-1088.
Information for Female Patients

What is Opsumit (macitentan)?
Opsumit is a prescription medicine used to treat pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of your lungs. Opsumit can improve your ability to exercise, improve some of your symptoms, and help slow down the progression of your disease. Opsumit can also lower your chance of being hospitalized for PAH.

It is not known if Opsumit is safe and effective in children.

What are the serious risks of Opsumit?
Opsumit can cause serious birth defects if taken during pregnancy. Women must not be pregnant when they start taking Opsumit or become pregnant while taking Opsumit.

What is the Opsumit REMS (Risk Evaluation and Mitigation Strategy) Program?
The Opsumit REMS Program is a program to tell patients and healthcare providers about the risk of serious birth defects when taking Opsumit. This program is required by the Food and Drug Administration (FDA). All females must enroll in the Opsumit REMS Program to receive Opsumit. REMS stands for Risk Evaluation and Mitigation Strategy.

If you are a female who can get pregnant, to receive Opsumit you must:
- Talk to your healthcare provider about the risks and benefits of Opsumit
- Read:
  a. The Opsumit Medication Guide
  b. The Opsumit REMS Guide for Females Who Can Get Pregnant
- Have a pregnancy test before you start taking Opsumit
- Have a pregnancy test before you receive your refill each month
- Use reliable forms of birth control during Opsumit treatment and for one month after stopping treatment with Opsumit
- Immediately notify your healthcare provider if you miss a menstrual period or suspect you are pregnant

Please see the necessary below to learn more about taking Opsumit and the Opsumit REMS Program.

Opsumit REMS Guide for Females Who Can Get Pregnant

Opsumit Medication Guide
Pharmacy Certification

Due to the risk of serious birth defects, Opsumit is only available through a network of certified pharmacies. For information on Opsumit certified pharmacies or wholesale distributors, please call Actelion Pathways® at 1-866-220-3546.

Outpatient Pharmacy Certification

Opsumit will be dispensed to outpatients by a limited number of certified pharmacies. Prior to dispensing Opsumit the pharmacy will confirm that the prescriber who wrote the prescription is enrolled, and if the patient is a female that she is enrolled in the Opsumit REMS Program. If either the female or prescriber is not enrolled, Opsumit will not be dispensed.

For Females of Reproductive Potential, pharmacies will:

- Ask the patient 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 pharmacist 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 healthcare provider immediately if her reproductive status changes

Females of Reproductive Potential and the 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.

Inpatient Pharmacy Certification

This inpatient pharmacy will:

- Establish systems, order sets, protocols or other measures to ensure the Opsumit REMS 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 inpatient setting until such time that registration has been completed
- Dispense no more than a 30-day (30 day temporary supply of Opsumit upon discharge of any patient
- Notify Actelion Pharmaceuticals LLC, Inc. ("Actelion") or FDA if any patient becomes pregnant during Opsumit treatment
- Not transfer Opsumit to any pharmacy, practice, 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

To enroll 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
- Agree that this pharmacy may be subject to an audit by the FDA, Actelion, or a designated third party
- Follow the completed form to Actelion Pathways at 1-866-220-3546

If an inpatient pharmacy needs Opsumit and is not enrolled in the Opsumit REMS Program, the inpatient pharmacy can contact Actelion Pathways at 1-866-220-3546 for assistance in obtaining a 35 day supply of Opsumit for a specific inpatient while initiating enrollment.

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.

To learn more about the serious risks associated with Opsumit, please refer to the resources below.
Enrollment Forms & Other Resources

Materials for Healthcare Providers
- Opsumit REMS Prescriber Enrollment and Agreement Form
- Opsumit Patient Enrollment and Consent Form
- Prescriber Guide for the Opsumit REMS Program
- Opsumit REMS Reproductive Potential Status Form

Materials for Female Patients
- Opsumit REMS Guide for Females Who Can Get Pregnant
- Opsumit Patient Enrollment and Consent Form
- Opsumit Medication Guide

Materials for Pharmacies
- Opsumit REMS Inpatient Pharmacy Enrollment Form

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