

Prescriber and Pharmacy Guide for the Opsumit[®] REMS Program

(Risk Evaluation and Mitigation Strategy)



Opsumit.
macitentan tablets 10 mg

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

ACTELION
Pathways[®]

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
- Prescribers must report any change or misclassification 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)
 - For the purposes of this REMS, females who have undergone tubal sterilization are classified as females of reproductive potential
- 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 Females: Females who have passed through 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
 - Females with other medical reasons for permanent, irreversible infertility
- For Females of Reproductive Potential:
 - Pregnancy must be ruled out prior to drug initiation, monthly during treatment, and one month after stopping treatment
 - 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 may 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 an *Opsumit REMS Prescriber Enrollment and Agreement Form* agreeing to follow the Opsumit REMS Program requirements. This form must be submitted to the Opsumit REMS Program.

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

Prescribers must determine whether the patient is a Female of Reproductive Potential or a Female of Non-Reproductive Potential (Pre-pubertal Female, Post-menopausal Female, or a female with other medical reasons for permanent, irreversible infertility). **This category must be documented on the *Opsumit REMS Patient Enrollment and Consent Form*.** (See definitions of Reproductive Potential Status.)

Based on whether the patient is a Female of Reproductive Potential or a Female of Non-Reproductive Potential (Pre-pubertal Female, Post-menopausal Female, or a female with other medical reasons for permanent, irreversible infertility), 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)

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

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

Prescriber's 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. **Determine** the reproductive potential of female patients
4. **Educate and counsel** female patients about the risks of Opsumit
5. **Enroll** female patients into the Opsumit REMS Program by completing an *Opsumit REMS Patient Enrollment and Consent Form*
6. **Check** patient's pregnancy status (if patient is a Female of Reproductive Potential)
7. **Monitor** pregnancy and reproductive potential status for female patients 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***
 - By signing the form, you attest to understanding the risks of Opsumit and agree to comply with the Opsumit REMS Program
3. **Determine the reproductive potential for female patients**
 - Prescribers should identify female patients (captured on the *Opsumit REMS 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
 - Female with other medical reasons for permanent, irreversible infertility

Definitions are provided in the section "Opsumit REMS Program overview."

4. **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 Females of Reproductive Potential (FRP), prescribers must:
 - Review with her the *Opsumit Medication Guide* and the *Opsumit REMS Guide for Females Who Can Get Pregnant*
 - 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
 - Counsel her to immediately contact her healthcare provider if she misses a menstrual period or suspects she is pregnant
 - Counsel her that she must agree to be contacted prior to each shipment to confirm that a pregnancy test has been completed
- For Females of Non-Reproductive Potential (FNRP)
 - For a Post-menopausal Female or a female with other medical reasons for permanent, irreversible infertility, prescribers must provide the *Opsumit Medication Guide*—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

5. **Enroll** female patients into the Opsumit REMS Program by completing the *Opsumit REMS 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

6. **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

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
 - Monitor patients' reproductive status during treatment with Opsumit and report any changes or misclassifications to the Opsumit REMS Program by completing and submitting the *Opsumit REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change
- For FNRPs, prescribers must:
 - Monitor patients' reproductive status during treatment with Opsumit and report any changes or misclassifications to the Opsumit REMS Program by completing and submitting the *Opsumit REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change
 - For each Pre-pubertal Female who is at least 8 years of age and older, annually verify and report the reproductive status by completing and submitting the *Opsumit REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*

Contraceptive 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.

- 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

Contraceptive options for Females of Reproductive Potential

Acceptable birth control options

Option 1	OR	Option 2	OR	Option 3	OR	Option 4
One method from this list:		One method from this list:		One method from this list:		One method from this list:
Standard intrauterine device (Copper T 380A IUD)		Estrogen and progesterone oral contraceptives ("the pill")		Diaphragm with spermicide		Partner's vasectomy
Intrauterine system (LNg 20 IUS: progesterone IUS)		Estrogen and progesterone transdermal patch		Cervical cap with spermicide		PLUS
Progesterone implant		Vaginal ring		PLUS		One method from this list:
Tubal sterilization		Progesterone injection		One method from this list:		Male condom
		PLUS		Male condom		Diaphragm with spermicide
		One method from this list:				Cervical cap with spermicide
		Male condom				Estrogen and progesterone oral contraceptives ("the pill")
		Diaphragm with spermicide				Estrogen and progesterone transdermal patch
		Cervical cap with spermicide				Vaginal ring
						Progesterone injection

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 Pathways*® at 1-866-228-3546.

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 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:

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

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

- Read the Opsumit Prescribing Information, *Opsumit Medication Guide*, and *Prescriber and Pharmacy Guide for the Opsumit REMS Program*
- Put processes and procedures in place to ensure the Opsumit REMS Program requirements are met
- Ensure training of dispensing staff on the Opsumit REMS Program procedures and materials, including the *Prescriber and Pharmacy Guide for the Opsumit REMS Program* prior to dispensing Opsumit
- Notify Actelion Pharmaceuticals US, Inc. ("Actelion") or FDA if any patient becomes pregnant during Opsumit treatment
- Develop a process to track compliance with the conditions above and provide information about its compliance to Actelion
- Agree that this pharmacy may be audited by the FDA, Actelion, or a designated third-party
- 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

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

To learn more about the serious risks associated with Opsumit, please refer to the full Prescribing Information including BOXED WARNING, *Opsumit Medication Guide*, and the *Prescriber and Pharmacy Guide for the Opsumit REMS Program* and the *Opsumit REMS Guide for Females Who Can Get Pregnant*. These materials are available at www.OpsumitREMS.com.

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 Opsumit® 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 Opsumit REMS Program,
please visit www.OpsumitREMS.com.

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