

Prescriber and Pharmacy Guide for the Opsumit[®] REMS

(Risk Evaluation and Mitigation Strategy)



Opsumit.
macitentan tablets 10 mg

*Please see accompanying full Prescribing Information,
including **BOXED WARNING** for embryo-fetal toxicity.*

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 reduce the risks of disease progression and 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 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 embryo-fetal toxicity

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 embryo-fetal toxicity effects when administered to animals. If Opsumit is used during pregnancy, advise the patient of the potential risk 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)

Due to the risk of embryo-fetal toxicity, Opsumit is only available to females through a restricted distribution program required by the FDA called the Opsumit REMS (**R**isk **E**valuation and **M**itigation **S**trategy).

The goal of the Opsumit REMS is to mitigate the risk of embryo-fetal toxicity associated with Opsumit by:

1. Ensuring prescribers are educated on the following:
 - the risks of embryo-fetal toxicity
2. Ensuring prescribers are educated on and adhere to the following:
 - counseling patients about these risks and the need for monthly monitoring
 - enrolling patients in the Opsumit REMS
 - monitoring patients at baseline and monthly
3. Ensuring that pharmacies are educated on the following:
 - the risks of embryo-fetal toxicity
4. Ensuring that pharmacies are educated on and adhere to the following:
 - confirming that the appropriate patient monitoring and counseling has occurred before dispensing Opsumit
5. Ensuring that patients are informed about:
 - the risks of embryo-fetal toxicity
 - appropriate baseline and monthly patient monitoring
 - appropriate contraception

Opsumit REMS overview

- All healthcare providers must enroll in the Opsumit REMS and comply with the requirements to prescribe Opsumit
- All female patients must enroll in the Opsumit REMS 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
- 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 can dispense Opsumit to outpatients
- Only inpatient pharmacies that are certified in the Opsumit REMS may stock Opsumit for inpatient use

Summary of Opsumit REMS requirements for female patients

All **prescribers** must be enrolled in the Opsumit REMS. To become enrolled, a healthcare provider must complete a *Prescriber Enrollment and Agreement Form* agreeing to follow the Opsumit REMS requirements. This form must be submitted to the Opsumit REMS, by faxing the completed form to 1-866-279-0669 **or** by calling *Actelion Pathways* at 1-866-228-3546.

All **females** must be enrolled in the Opsumit REMS in order to receive Opsumit. To become enrolled, a patient must complete a *Patient Enrollment and Consent Form* with her prescriber. This form must be submitted to the Opsumit REMS, and can be completed online at OpsumitREMS.com, **or** by calling *Actelion Pathways* at 1-866-228-3546, **or** by faxing the completed form to 1-866-279-0669.

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 *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 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	●	●	●
Prescriber counsels with <i>Guide for Female Patients</i>	●	●*	●
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>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

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

1. **Read** the Opsumit Prescribing Information and this guide to understand the risks of Opsumit and to learn about the Opsumit REMS
2. **Complete** a *Prescriber Enrollment and Agreement Form*
3. **Determine** the reproductive potential of female patients
4. **Educate and counsel** all female patients about the risks of Opsumit
5. **Enroll** female patients into the Opsumit REMS by completing an *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**
 - Prescribers must understand the risks of Opsumit and become familiar with the Opsumit REMS
2. **Complete a *Prescriber Enrollment and Agreement Form***
 - You can download the *Prescriber Enrollment and Agreement Form* from OpsumitREMS.com and fax it to Actelion Pathways® at 1-866-279-0669 **or** you may enroll by calling Actelion Pathways at 1-866-228-3546. Actelion Pathways administers the Opsumit REMS. After providing your enrollment by phone you will receive a pre-populated form by fax to sign and fax to 1-866-279-0669.
 - By signing the form, you attest to understanding the risks of Opsumit and agree to comply with the Opsumit REMS
3. **Determine the reproductive potential for female patients**
 - Prescribers should identify female patients (captured on the *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 Overview."

4. **Educate and counsel** all 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
 - Educate and counsel patients about the risks of Opsumit
- For Females of Reproductive Potential (FRP), prescribers must:
 - Review with her the *Guide for Female Patients*
 - Educate her about the risk of embryo-fetal toxicity; 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 *Guide for Female Patients* and instruct her to read it
 - For Pre-pubertal Females, prescribers must:
 - Review with her and her parent/guardian the *Guide for Female Patients*
 - 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 by completing the *Patient Enrollment and Consent Form*

- Enroll a patient **online**
 - For immediate patient enrollment, please go to OpsumitREMS.com
 - Confirm patient has agreed to comply with program requirements and has signed the form where indicated
 - Patients can sign electronically at the time of enrollment by typing their name into the signature box, or signing with their finger or stylus on touchscreen devices. Patients can also provide their email address to provide an electronic signature later. Print the form and keep with the patient’s records
- Enroll a patient **by fax** using the printed form
 - Download the *Patient Enrollment and Consent Form* from OpsumitREMS.com
 - Confirm patient has agreed to comply with program requirements and has signed the form where indicated
 - Fax the completed form to *Actelion Pathways*® at 1 866-279-0669. *Actelion Pathways* administers the Opsumit REMS
 - Keep the original form with the patient’s records
- Enroll a patient by **calling** *Actelion Pathways* at 1-866-228-3546
 - Confirm patient has agreed to comply with program requirements and provided their verbal consent by calling *Actelion Pathways* at 1-866-228-3546
 - Sign the pre-populated form faxed by *Actelion Pathways* and fax the signed and completed form to *Actelion Pathways* at 1 866-279-0669
 - Keep the signed form with the patient’s records

Note: Enrollment by phone and online enrollment are not available for VA patients.

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 (1) 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 by completing and submitting the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change **or** by contacting *Actelion Pathways*® at 1-866-228-3546
- For FNRPs, prescribers must:
 - Monitor patients’ reproductive status during treatment with Opsumit and report any changes or misclassifications to the Opsumit REMS by completing and submitting the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* **or** by contacting *Actelion Pathways* at 1-866-228-3546 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 *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* **or** by contacting *Actelion Pathways* at 1-866-228-3546

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 following table for a complete list of acceptable contraceptive methods. A similar table can be found in the *Guide for Female Patients* and should be used to discuss acceptable birth control options with patients. The patient should be instructed to select one of the options listed.

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

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.

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. 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
- Dispense to a female patient only after she has been enrolled in the Opsumit REMS 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, an authorized representative of the inpatient pharmacy must:

- Read the Opsumit Prescribing Information and *Prescriber and Pharmacy Guide*
- Put processes and procedures in place to ensure the Opsumit REMS requirements are met
- Ensure training of dispensing staff on the Opsumit REMS procedures and materials, including the *Prescriber and Pharmacy Guide* prior to dispensing Opsumit
- Enroll in the Opsumit REMS if the inpatient pharmacy designates a new authorized representative by completing, signing, and submitting a new ***Inpatient Pharmacy Enrollment Form*** as soon as the designated authorized representative changes
- 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 *Inpatient Pharmacy Enrollment Form* to the Opsumit REMS
 - Authorized representatives can complete the *Inpatient Pharmacy Enrollment Form*:
 - By faxing the printed form to 1-866-279-0669
 - By calling the Opsumit REMS at 1-866-228-3546

If an inpatient pharmacy needs Opsumit and is not enrolled in the Opsumit REMS, 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, the *Prescriber and Pharmacy Guide*, and the *Guide for Female Patients*. 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 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,
please visit www.OpsumitREMS.com

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