Initial REMS Approval: 10/2013

NDA 204410

OPSUMIT® (macitentan)
Endothelin Receptor Antagonist

Sponsor: Actelion Pharmaceuticals Ltd
Contact: Actelion Clinical Research Inc
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Cherry Hill, NJ 08002
[856-773-4300]

Risk Evaluation and Mitigation Strategy (REMS)

I. GOALS:

The goals of the Opsumit Risk Evaluation and Mitigation Strategy (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 full prescribing information (PI), the Opsumit Medication Guide, and the *Prescriber 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 Guide for the Opsumit REMS Program*

v. For FRP (as defined by the *Prescriber 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 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 in reproductive status by completing the *Opsumit REMS Reproductive Potential Status Form* within ten (10) business days of becoming aware of the change

vi. For females of non-reproductive potential (FNRP) (as defined by the *Prescriber 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 and the need to use reliable contraception, once the patient becomes a FRP as defined in the *Prescriber Guide for the Opsumit REMS Program,* during Opsumit treatment, and for one month following treatment discontinuation

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 Reproductive Potential Status Form* verifying their reproductive potential status

e) Report a change in reproductive status by completing the *Opsumit REMS Reproductive Potential Status Form* within ten (10) business days of becoming aware of the change

2) Post-menopausal patients:

a) Report a change in reproductive status by completing the *Opsumit REMS Reproductive Potential Status Form* within ten (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.

c. The following are part of the REMS and are appended:

i. Opsumit Patient Enrollment and Consent Form

ii. Opsumit REMS Guide for Females Who Can Get Pregnant

iii. Prescriber Guide for the Opsumit REMS Program

iv. Opsumit REMS Prescriber Enrollment and Agreement Form

v. Opsumit REMS Reproductive Potential Status Form

vi. Opsumit REMS Website

2. **Pharmacies, practitioners, and healthcare settings (dispensers) that dispense Opsumit will be specially certified**

Outpatient Dispensing

a. Actelion will ensure that pharmacies, practitioners, and healthcare settings that dispense Opsumit are specially certified. Actelion will ensure that to be certified pharmacies, practitioners, and healthcare settings that dispense Opsumit attest that they will:

   i. Receive and accept the *Opsumit Patient Enrollment and Consent Form* only from Actelion Pathways

   ii. Dispense Opsumit only to patients who have a prescription written by a prescriber enrolled in the Opsumit REMS Program

   iii. Dispense Opsumit to females only if they are enrolled in the Opsumit REMS program

   iv. Only dispense up to a 30-day supply of Opsumit to pre-pubertal females and FRP

   v. Verify reproductive status of females with information provided by Actelion Pathways prior to each dispensing of Opsumit

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

   vii. 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 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

viii. Notify Actelion of any reports of pregnancy and provide all available information

b. Actelion will ensure that an authorized representative of each certified dispenser:

i. Is trained on the Opsumit REMS program

ii. Trains dispensing staff on the Opsumit REMS program procedures and Opsumit REMS materials prior to dispensing Opsumit

iii. Agrees that the certified dispenser may be audited by the FDA, Actelion, or a third party designated by Actelion

c. Actelion will ensure that Actelion Pathways notifies certified dispensers of a patient's change in reproductive status within one business day of awareness of a change.

Inpatient Dispensing

a. Only inpatient pharmacies (including, but not limited to, 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.

i. 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:

1) Establish systems, order sets, protocols, or other measures to ensure the REMS requirements are met

2) Dispense Opsumit only to patients under the supervision and care of a healthcare provider who is enrolled in the Opsumit REMS program

3) 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

4) Dispense no more than a 15 day temporary supply of Opsumit, to any patient, upon discharge from the healthcare facility

5) Notify Actelion of any reports of pregnancy during Opsumit treatment and provide all available information

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

7) Develop a process to track compliance with the conditions above and provide information about compliance to Actelion upon request

b. If an inpatient pharmacy needs Opsumit for a specific inpatient and is not enrolled in the Opsumit REMS Program, the inpatient pharmacy should contact Actelion Pathways for assistance in obtaining up to a 15 day supply of Opsumit for a specific inpatient while initiating enrollment.

c. Actelion will ensure that an authorized representative of each inpatient pharmacy:

   i. Is trained on the Opsumit REMS program

   ii. Assumes responsibility for the training of dispensing staff on the Opsumit REMS program requirements and Opsumit REMS materials prior to dispensing Opsumit

   iii. Agrees that the inpatient pharmacy may be audited by the FDA, Actelion, or a third party designated by Actelion

d. The following materials are part of the REMS and are appended:

   i. Opsumit REMS Inpatient Pharmacy Enrollment Form

3. Opsumit will be dispensed to females with evidence or other documentation of safe use conditions

a. Actelion will ensure that to become enrolled, each female signs the *Opsumit Patient Enrollment and Consent Form*.

b. By completing the *Opsumit Patient Enrollment and Consent Form*, FRPs will 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 patients registered in the Opsumit REMS Program.
4. Actelion will audit all certified outpatient dispensers within 180 days after the Opsumit REMS approval to ensure they implement the Opsumit REMS Program as directed. Thereafter, Actelion will include the certified outpatient dispensers in the company's annual audit plan.
5. Actelion will monitor and evaluate implementation of elements provided under Section B.2. and B.3. above in the manner described in the Opsumit REMS supporting document and if needed, take steps to improve implementation of these elements.
6. 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.
7. Actelion will audit Actelion Pathways within 180 days after the Opsumit REMS approval to ensure they implement the Opsumit REMS Program as directed. Thereafter, Actelion will include Actelion Pathways in the company's annual audit plan.

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.

Opsumit® Patient Enrollment and Consent Form

Complete this form for ALL patients

Fax this completed form and copies of all insurance cards (front and back) to 1-866-279-0669.

Contact Actelion Pathways™ at 1-866-228-3546 for questions.

EO1201310

1 Patient Information (please print)

First name ____ MI ____ Last name ____ Gender ☐ Male ☐ Female

Birth date ____ Primary language ____ Email address ____

Primary phone # ____ Alternate phone # ____ Best time to call ____

Address ____ City ____ State ____ ZIP ____

Legal guardian ____ Relationship ____ Phone # ____

Emergency contact ____ Relationship ____ Phone # ____

Certified pharmacy preference (If left blank, this referral will be sent to the appropriate certified pharmacy based on the patient's existing benefits.)

2 Actelion Pathways Services Authorization

I allow my healthcare providers and health plans to share my personal and health information about me and my Actelion therapies with Actelion and its contractors. I allow Actelion to use and share this information to: 1) establish my benefit eligibility, including benefit eligibility for laboratory services; 2) communicate with my healthcare providers, health plans, other payers, and pharmacies about my medical care; and 3) help provide any therapy access support services to me that will assist in my Actelion therapy. Actelion may leave messages for me on the telephone number(s) that I provide. These messages may state that I take an Actelion medication as well as provide me with additional information. I also allow the sharing of my health information to specific people I have identified.

I understand that Actelion does not promise to find ways to pay for my medications. I know that I am responsible for the costs of my care. I understand that once my health information has been shared with Actelion, privacy laws may no longer protect it; however, Actelion agrees to protect my information by using and sharing it only for reasons listed above or as required by law. I understand that my certified pharmacy may receive payment in connection with the use and disclosure of my information for purposes allowed under this permission. If I do not sign this form, my eligibility for health plan benefits and treatment by my healthcare provider will not change, but I will not have access to the Actelion support services. I may also cancel my permission at any time by writing a letter saying I cancel my written permission and mailing to Actelion Pharmaceuticals US, Inc.: PO Box 826, South San Francisco, CA 94083 or by faxing it to 1-866-279-0669 or by calling 1-866-228-3546. I am allowed a copy of this signed agreement. This written permission will expire 10 years after the date on which I sign it.

★ ____ **(REQUIRED FOR ALL PATIENTS)** Patient or Parent/Guardian Signature ____ Date

3 Female Patient Agreement

For All Females: I acknowledge that I understand that Opsumit is only available through a restricted distribution program under an FDA-required Risk Evaluation and Mitigation Strategy (REMS).

For Females Who Can Get Pregnant: I acknowledge that I have been counseled on the risks of Opsumit, including the risk of serious birth defects. I have read the *Opsumit Medication Guide* and the *Opsumit REMS Guide for Females Who Can Get Pregnant*. I understand that I will be contacted by Actelion and/or its agents and contractors to receive counseling on the risk of serious birth defects, the need to use reliable contraception during Opsumit treatment and for one month after stopping Opsumit treatment, the importance of not becoming pregnant, and to ensure that I have completed pregnancy testing before I start Opsumit, monthly before each refill, and for one month after stopping Opsumit. I agree 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. I understand that I must immediately contact my healthcare provider if I miss a menstrual period or suspect that I am pregnant; and that I may be contacted by Actelion and/or its agents and contractors to obtain information about my pregnancy, if I become pregnant.

For Pre-pubertal Females: I acknowledge that I have been counseled on the risks of Opsumit, including the risk of serious birth defects, and that I have read the *Opsumit Medication Guide*. I understand that I must immediately contact my healthcare provider if I get my menstrual period.

For Post-menopausal Females: I acknowledge that I have received and read the *Opsumit Medication Guide*.

★ ____ **(REQUIRED FOR ALL FEMALES)** Patient or Parent/Guardian Signature ____ Date

4 Prescriber Information

First name ____ Middle initial ____

Last name ____

Address ____ City ____

State ____ ZIP ____ Phone # ____

Fax ____ NPI # ____

Opsumit ID ____

Office contact and email address ____

5 Diagnosis, Prescription, and Shipping Information

(Check ONLY ONE Box for the Diagnosis Related to Opsumit Treatment)

Pulmonary Arterial Hypertension (PAH)

☐ Idiopathic PAH ☐ Heritable PAH ☐ Connective Tissue Disorder ☐ Congenital Heart Disease

☐ Other ____

Opsumit (macitentan) dosing: 10 mg tablet(s) NDC66215-501-30

____ Time(s) daily Quantity: ____ Refills: ____

Instructions for use: ____

Ship to: ☐ Patient home ☐ Prescriber office ☐ Other

Address ____

City ____ State ____ ZIP ____

6 Prescriber Authorization

If your patient is FEMALE, check correct female patient category (please see definitions of these terms on the following page):

REQUIRED (Check one box)

Female of Reproductive Potential

If this patient is a Female of Reproductive Potential, has a negative pregnancy test been completed prior to prescribing Opsumit?

☐ Yes ☐ No

Female of Non-Reproductive Potential

☐ **Pre-pubertal Female** ☐ **Post-menopausal Female**

I certify that the above therapy is medically necessary and agree to follow the "Prescriber Requirements" indicated on the second page of this form.

★ ____ **(REQUIRED FOR ALL PRESCRIBERS)** Prescriber signature ____ Date

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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.

Prescriber Requirements

For All Females

- I acknowledge that I have counseled the patient (and parent/guardian when appropriate) that Opsumit is only available through a restricted distribution program under an FDA-required REMS
- I will evaluate the patient and agree to document any change in reproductive potential status by submitting a *Opsumit REMS Reproductive Potential Status Form* within 10 business days of becoming aware of the change

For Females of Reproductive Potential

- I acknowledge that I have counseled the patient (and parent/guardian when appropriate) on the risks of Opsumit, including the risk of serious birth defects, and that I have reviewed the *Opsumit Medication Guide* and the *Opsumit REMS Guide for Females Who Can Get Pregnant* with the patient (and parent/guardian when appropriate)
- I will order and review pregnancy tests prior to initiation of Opsumit treatment, monthly during treatment, and for 1 month after stopping treatment in accordance with the Opsumit REMS Program

For Pre-pubertal Females

- I acknowledge that I have counseled the patient and parent/guardian on the risks of Opsumit, including the risk of serious birth defects, and that I have reviewed the *Opsumit Medication Guide* with the patient and parent/guardian
- I will evaluate the patient's reproductive potential status, verify reproductive potential status annually for Pre-pubertal Females who are at least 8 years of age and older, and agree to report any change in reproductive potential status on a *Opsumit REMS Reproductive Potential Status Form* within 10 business days of becoming aware of the change

7 Fax this form to 1-866-279-0669

Please visit www.OpsumitREMS.com or call 1-866-ACTELION (1-866-228-3546) for more information about the Opsumit REMS Program.

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Opsumit® REMS (Risk Evaluation and Mitigation Strategy) Guide for Females Who Can Get Pregnant

Information to help you throughout your treatment with Opsumit

Opsumit®
macitentan tablets 10 mg

Please see accompanying full Prescribing Information, including ***BOXED WARNING*** *for birth defects, and Medication Guide.*

ACTELION Pathways™

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What is Opsumit?

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.

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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,
- While taking Opsumit, or
- Within one month of stopping Opsumit.

What is the Opsumit REMS (Risk Evaluation and Mitigation Strategy) Program?

The Opsumit REMS 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 **R**isk **E**valuation and **M**itigation ***S***trategy.

How do I enroll in the Opsumit REMS Program?

There are several steps you must take:

1. Read this *Opsumit REMS Guide for Females Who Can Get Pregnant* and the *Opsumit Medication Guide* (which comes with your medicine).
2. Ask your healthcare provider any questions you have about taking Opsumit and the Opsumit REMS Program.
3. Make sure you understand:

   – The benefits and risks of Opsumit

   – How to enroll and take part in the Opsumit REMS Program
4. Complete and sign the *Opsumit Patient Enrollment and Consent Form* with your healthcare provider. Your healthcare provider will fill out most of the enrollment form for you and will send the form to Actelion Pathways. Actelion Pathways runs the Opsumit REMS Program.

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What are the Opsumit REMS Program requirements for me?

- Females who can get pregnant must have a negative pregnancy test before starting Opsumit, each month for as long as they are being treated with Opsumit, and for one month after they stop taking Opsumit. Your healthcare provider will order the pregnancy tests for you.
  - You are considered a female who can get pregnant if you:
    - Have entered puberty, even if you have not started your period, and
    - Have a uterus, and
    - Have not gone through menopause (have not had a period for at least 12 months for natural reasons, or have had your ovaries removed)
- Opsumit is not available at your local pharmacy. You must receive Opsumit through a certified pharmacy (sometimes called a specialty pharmacy).
  - Your pharmacy will call you every month to ask if you have completed a pregnancy test before shipping your Opsumit to your home or another shipping address you choose.
  - You may not receive your Opsumit refill on time if you do not confirm with the pharmacy that you have had your monthly pregnancy test
- You must use reliable birth control at all times when taking Opsumit and for one month after stopping Opsumit. Your birth control options are listed on page 5.
- Do not have unprotected sex.
- Talk to your healthcare provider right away if you have unprotected sex, if you think your birth control has failed, or if you think you are pregnant. If so, your healthcare provider may discuss medical options with you (e.g. emergency contraception). Do not wait until your next appointment to tell your healthcare provider if you miss your menstrual period or if you think you are pregnant.

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What are my birth control options?

Your healthcare provider will talk with you about your birth control options before starting Opsumit. Ask your healthcare provider if you have any questions. Tell your healthcare provider if you want to change your birth control.

You must choose one of the 4 options listed below. More than one birth control method might be needed every time you have sex.

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 One method from this list:**
Progesterone implant		Vaginal ring		**PLUS One method from this list:**		Male condom
Tubal sterilization		Progesterone injection		Male condom		Diaphragm with spermicide
		PLUS 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

How will I receive Opsumit?

Opsumit is available only through certified pharmacies.

- Actelion Pathways provides support and services that help patients with their PAH medicines. Once you are enrolled, a Patient Case Manager will work with you to get your Opsumit prescription filled by a pharmacy.
- Before your first prescription is filled, the pharmacy will call you to schedule a shipment of Opsumit that will come right to your home.
- The *Opsumit Medication Guide* will be included in the package.
- Read the *Opsumit Medication Guide* each time you receive it. Important information may have been added or changed.

For a list of certified pharmacies, please call Actelion Pathways at **1-866-ACTELION (1-866-228-3546)**.

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Your steps to treatment with Opsumit

Use this helpful checklist to get started with Opsumit and to stay on track during your treatment.

FIRST:

- ☐ Review the *Opsumit REMS Guide for Females Who Can Get Pregnant* and the *Opsumit Medication Guide* with your healthcare provider
- ☐ Make sure you understand the risks and benefits of taking Opsumit
- ☐ Go for your pregnancy test
- ☐ Register in the Opsumit REMS Program

NEXT:

- ☐ Expect a call from your Patient Case Manager. He or she will help you get your Opsumit prescription filled by one of the certified pharmacies
- ☐ Expect a call from the pharmacy to schedule your first shipment

EVERY MONTH:

- ☐ Read the *Opsumit Medication Guide* that comes with every shipment
- ☐ Use reliable birth control method(s) agreed upon with your healthcare provider—during treatement and for one month after you stop taking Opsumit
- ☐ Take the monthly pregnancy test ordered by your healthcare provider
- ☐ Expect your pharmacy to call you every month to ask if you had a pregnancy test in the last month before it reorders your Opsumit. The refill may not be done on time if you've not had your pregnancy test.
- ☐ Do not get pregnant. Tell your healthcare provider right away if you:
  - – Have unprotected sex
  - – Think that your birth control failed
  - – Miss a menstrual period
  - – Think you are pregnant

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The Opsumit REMS Program is administered by Actelion Pathways™.

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

For more information about the Opsumit REMS Program, please visit www.OpsumitREMS.com

Please see accompanying full Prescribing Information, including* BOXED WARNING *for birth defects, and Medication Guide.

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Prescriber Guide for the Opsumit® REMS Program

(Risk Evaluation and Mitigation Strategy)

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

ACTELION Pathways™

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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%).

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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 (**R**isk **E**valuation and **M**itigation **S**trategy) 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.

Reference ID: 3392795

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.

Reference ID: 3392795

Summary of Opsumit® REMS Program requirements for female patients (continued)

Requirement	Females of Reproductive Potential	Females of Non-Reproductive Potential	
		Pre-pubertal	Post-menopausal
Prescriber enrolls female patients into Opsumit REMS Program	●	●	●
Prescriber counsels with *Opsumit REMS Guide for Females Who Can Get Pregnant*	●		
Prescriber counsels with *Opsumit Medication Guide*, 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 *Opsumit REMS Reproductive Potential Status Form*		●	
Prescriber must complete the *Opsumit REMS Reproductive Potential Status Form* upon becoming aware of any change in reproductive potential status within 10 business days of awareness	●	●	●

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

Reference ID: 3392795

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

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:
     - 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.

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– 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

Option 1		Option 2		Option 3		Option 4
One method from this list:	OR	**One method from this list:**	OR	**One method from this list:**	OR	**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 One method from this list:**
Progesterone implant		Vaginal ring		**PLUS One method from this list:**		Male condom
Tubal sterilization		Progesterone injection		Male condom		Diaphragm with spermicide
		PLUS 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

Reference ID: 3392795

- 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.

Reference ID: 3392795

- 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

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 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 OpsumitREMS.com

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

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Opsumit® REMS Prescriber Enrollment and Agreement Form

Please complete and fax this form to Actelion Pathways™ at 1-866-279-0669.

You can also reach Actelion Pathways via phone at 1-866-ACTELION (1-866-228-3546)

PO1201310

Prescriber Information (please print)

First name | MI | Last name

Email address | NPI # | ☐ MD ☐ DO ☐ PA ☐ NP Professional designation

In the event you are unavailable, is there another person we can contact on your behalf? ☐ Yes ☐ No
If yes, please indicate.

Name | Phone

Office Practice/Clinic Information (please print)

Primary

Office practice/Clinic name | Affiliated hospital

Specialty | Office contact name | Office contact phone

Office email address | Phone | Fax

Address | City

State | ZIP | ☐ Phone ☐ Fax ☐ Email Preferred method of contact

Secondary

Office practice/Clinic name | Affiliated hospital

Specialty | Office contact name | Office contact phone

Office email address | Phone | Fax

Address | City

State | ZIP | ☐ Phone ☐ Fax ☐ Email Preferred method of contact

Opsumit REMS Prescriber Agreement

By signing below, you signify your understanding of the risks of Opsumit treatment and your obligation as an Opsumit prescriber to educate your female patients about the Opsumit REMS (Risk Evaluation and Mitigation Strategy) Program, monitor them appropriately, and report any pregnancies to the Opsumit REMS Program.

Specifically, you attest to the following:

- I have read the full Prescribing Information, the Opsumit *Medication Guide*, and the *Prescriber Guide for the Opsumit REMS Program* and agree to comply with the Opsumit REMS Program requirements
- I agree to enroll all female patients into the Opsumit REMS Program
- I will:
  - Determine the reproductive potential status of all female patients using the definitions provided in the *Prescriber Guide for the Opsumit REMS Program*
  - Advise all females that Opsumit is only available through a restricted distribution program called the Opsumit REMS Program
  - Counsel Females of Reproductive Potential (FRP) on the risks of Opsumit, including the risk of serious birth defects, and review the *Opsumit Medication Guide* and the *Opsumit REMS Guide for Females Who Can Get Pregnant* with the patient
  - Counsel the Pre-pubertal Female patients and parent/guardian on the risks of Opsumit, including the risk of serious birth defects, and review the *Opsumit Medication Guide* with the patient and parent/guardian
  - Counsel FRPs to immediately contact their healthcare provider if they miss a menstrual period or suspect pregnancy
  - Verify the reproductive potential status annually for Pre-pubertal Females who are at least 8 years of age and older
  - Order and review pregnancy tests for Females of Reproductive Potential prior to initiating treatment with Opsumit, monthly during treatment, and for one month after stopping treatment
  - Counsel FRPs to use reliable contraception during Opsumit treatment, and for one month after stopping treatment; and discuss their medical options in the event of unprotected sexual intercourse or known or suspected contraceptive failure
  - Report any change in reproductive potential status by submitting an *Opsumit REMS Reproductive Potential Status Form* within 10 business days of becoming aware of the change
  - Counsel female patients who fail to comply with the Opsumit REMS Program requirements
  - Notify the Opsumit REMS Program of any pregnancies at 1-866-ACTELION (1-866-228-3546)

Signature | Date

Please visit www.OpsumitREMS.com or call 1-866-ACTELION (1-866-228-3546) for more information about the Opsumit REMS Program.

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Opsumit® REMS Reproductive Potential Status Form

Complete this form to:

1) Change the reproductive status of any female patient within 10 business days of awareness of the change in reproductive status

2) Complete the annual verification of the reproductive potential status for Pre-pubertal Females 8 years of age or older

Fax this form to Actelion Pathways™ at 1-866-279-0669.

Prescriber must complete this form within 10 business days of awareness of the change in reproductive status.

Patient Information (please print)

Patient Opsumit ID

First name | MI | Last name

Address

City | State | ZIP

Birth date | Phone

Prescriber Information (please print)

First name | MI | Last name

NPI #

Address

City | State | ZIP

Phone | Fax

Opsumit Prescriber ID (if available)

Office contact and email address (optional)

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.

Select the most appropriate reason for submitting this form.

(For reference, please see the Definitions of Reproductive Potential Status)

Annual Verification

☐ Patient remains a Pre-pubertal Female (8 years of age or older)

Change in Status (check ONE box)

Patient is a Female of Reproductive Potential because:

☐ Patient is a female who has entered puberty, or

☐ Patient was previously misclassified

Patient is a Female of Non-Reproductive Potential (excluding Pre-pubertal Females) because:

☐ Patient is Post-menopausal, or

☐ Patient was previously misclassified, and is now Pre-pubertal, or

☐ Patient was previously misclassified, and is now Post-menopausal

Prescriber acknowledgement (REQUIRED)

By signing, I certify that the patient's reproductive status as noted above is accurate, and that I will comply with the REMS requirements for my patient's reproductive potential status.

Prescriber signature | Title (MD/PA/NP, etc) | Date

Please visit www.OpsumitREMS.com or call 1-866-ACTELION (1-866-228-3546) for more information about the Opsumit REMS Program.

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Reference ID: 3392795

FO1201310

Opsumit® REMS Inpatient Pharmacy Enrollment Form

Please complete and fax this form to Actelion Pathways™ at 1-866-279-0669.

You can also reach Actelion Pathways via phone at 1-866-ACTELION (1-866-228-3546)

HO1201310

Due to the risk of teratogenicity for female patients, Opsumit is available only through a restricted program called the Opsumit REMS (Risk Evaluation and Mitigation Strategy) Program. In order for inpatients to receive Opsumit, females, as well as inpatient pharmacies that wish to stock this product, must enroll in the Opsumit REMS Program and agree to comply with the requirements of the program. An Authorized Representative must complete and submit this form on behalf of the inpatient pharmacy.

Inpatient pharmacy information (please print)

Name

☐ Hospital ☐ Nursing home ☐ Hospice ☐ Asylum/Mental facility ☐ Assisted Living ☐ Prison ☐ Rehabilitation

☐ Other (please specify): _____

Identification (please complete one of the following):

☐ Health Industry Number (HIN #) _____ ☐ National Provider Identifier (NPI #) _____

☐ Other identifier: _____

Address

City State ZIP

Phone # Fax #

Ship to address (if different from above)

Address

City State ZIP

Phone # Fax #

Authorized Representative information (please print)

Name

Title:

☐ Hospital pharmacist ☐ Head of Pharmacy and Therapeutics (P&T) committee

☐ Other title: _____

Authorized Representative phone # Fax #

Authorized Representative email

Authorized Representative consent

This inpatient pharmacy will:

- 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

I attest that I have read the Opsumit full *Prescribing Information*, *Medication Guide*, and *Prescriber Guide for the Opsumit REMS Program* available at www.OpsumitREMS.com.

I will ensure training of dispensing staff on the Opsumit REMS Program procedures and materials prior to dispensing Opsumit.

I agree that this pharmacy may be audited by the FDA, Actelion, or a designated third-party.

Note: If your inpatient pharmacy needs Opsumit and is not enrolled in the Opsumit REMS Program, 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.

Signature Date

Please visit www.OpsumitREMS.com or call 1-866-ACTELION (1-866-228-3546) for more information about the Opsumit REMS Program.

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Opsumit Risk Evaluation and Mitigation Strategy (REMS) Program

Opsumit REMS (Risk Evaluation and Mitigation Strategy) Program

A Risk Evaluation and Mitigation Strategy (REMS) is a program required by the Food and Drug Administration (FDA) to manage serious risks associated with a drug product.

The Opsumit REMS Program is for females only. Male patients are not required to enroll in the Opsumit REMS Program.

The goals of the Opsumit REMS are:

- To inform prescribers, patients, and pharmacists about the risk of serious birth defects and safe-use conditions for Opsumit
- To minimize the risk of fetal exposure and adverse fetal outcomes in females of reproductive potential prescribed Opsumit:
  a. Females who are pregnant must not be prescribed Opsumit
  b. Females taking Opsumit must not become pregnant

Materials for Healthcare Providers

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

Prescribers

For Prescriber Information **Click Here**

Female Patients

For Patient Information **Click Here**

Materials for Female Patients

- *Opsumit REMS Guide for Females Who Can Get Pregnant*
- *Opsumit Medication Guide*

Opsumit REMS Program Overview:

- All healthcare providers must enroll in the Opsumit REMS Program and comply with requirements to prescribe Opsumit
- All female patients must be enrolled in the Opsumit REMS Program to receive Opsumit
- Females of Reproductive Potential and Pre-pubertal Females of Non-Reproductive Potential are required to be counseled on the risks of Opsumit
- Females of Reproductive Potential are required to get monthly pregnancy testing
- A limited number of certified pharmacies will dispense Opsumit for outpatients. They must enroll in the Opsumit REMS Program and agree to the REMS requirements
- Pharmacies that supply inpatient use of Opsumit must also be certified by enrolling in the Opsumit REMS Program and agreeing to the REMS requirements

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%).

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Opsumit Risk Evaluation and Mitigation Strategy (REMS) Program

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 Enrollment 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 Enrollment and Agreement Form* here and fax it to Actelion Pathways™ at 1-866-279-0669. Actelion Pathways administers the Opsumit REMS Program

3. **Enroll female patients into the Opsumit REMS Program by completing the** *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 to Actelion Pathways at 1-866-279-0669. 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 Enrollment and Consent Form*) as one of the following categories:
     a. Female of Reproductive Potential
     Or
     b. Female of Non-Reproductive Potential (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 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 (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 she 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:
     a. Advise the patient that Opsumit is only available through a restricted distribution program called the Opsumit REMS Program
     b. Educate and counsel patients about the risks of Opsumit
     - For Females of Reproductive Potential, 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 serious birth defects;
         - 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 Females of Non-Reproductive Potential, 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 Females of Reproductive Potential, prescribers must:
     a. Order and review pregnancy tests monthly during treatment with Opsumit and for one month after stopping treatment
     b. Notify the patient and Actelion if a patient's pregnancy test is positive
   - For Females of Non-Reproductive Potential, prescribers must:
     a. 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
     a. 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*

PDF Prescriber Guide for the Opsumit REMS Program

PDF Opsumit Patient Enrollment and Consent Form

PDF Opsumit REMS Prescriber Enrollment and Agreement Form

PDF Opsumit REMS Reproductive Potential Status Form

Reporting to Actelion
To report any pregnancies and suspected adverse reactions, contact Actelion at 1-866-228-3546.

Reporting to FDA MedWatch
Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

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Opsumit Risk Evaluation and Mitigation Strategy (REMS) Program

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* and
  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 resources below to learn more about taking Opsumit and the Opsumit REMS Program.

PDF Opsumit REMS Guide for Females Who Can Get Pregnant

PDF Opsumit Medication Guide

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Opsumit Risk Evaluation and Mitigation Strategy (REMS) Program

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 1-866-228-3546.

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 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 healthcare provider immediately if her reproductive status changes

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.

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 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

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
- Fax the completed form to Actelion Pathways at 1-866-279-0669

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.

PDF Opsumit REMS Inpatient Pharmacy Enrollment Form

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.

PDF Opsumit Prescribing Information

PDF Opsumit Medication Guide

PDF Prescriber Guide for the Opsumit REMS Program

PDF Opsumit REMS Guide for Females Who Can Get Pregnant

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Opsumit Risk Evaluation and Mitigation Strategy (REMS) Program

Enrollment Forms & Other Resources

Materials for Healthcare Providers

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

Materials for Female Patients

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

Materials for Pharmacies

- PDF Opsumit REMS Inpatient Pharmacy Enrollment Form

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