Prescriber and Pharmacy Guide for the Macitentan REMS
(Risk Evaluation and Mitigation Strategy)
Introduction to macitentan

Indication

Macitentan 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

Macitentan is contraindicated in females who are pregnant. Macitentan may cause fetal harm when administered to a pregnant woman. Macitentan was consistently shown to have embryo-fetal toxicity effects when administered to animals. If macitentan 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 macitentan. Patients must not become pregnant while taking macitentan.

Macitentan REMS (Risk Evaluation and Mitigation Strategy)

Due to the risk of embryo-fetal toxicity, macitentan is only available to females through a restricted distribution program required by the FDA called the Macitentan REMS (Risk Evaluation and Mitigation Strategy).

The goal of the Macitentan REMS is to mitigate the risk of embryo-fetal toxicity associated with macitentan 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 Macitentan 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 macitentan
5. Ensuring that patients are informed about:
   - the risks of embryo-fetal toxicity
   - appropriate baseline and monthly patient monitoring
   - appropriate contraception
Macitentan REMS overview

• All healthcare providers must certify by enrolling in the Macitentan REMS and comply with the requirements to prescribe macitentan

• All female patients must enroll in the Macitentan REMS to receive macitentan

• Prescribers must counsel females of reproductive potential and pre-pubertal females of non-reproductive potential about the risks of macitentan, 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 Macitentan REMS

• Definitions of reproductive potential status
  – Females of reproductive potential
    o 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)
    o For the purpose of this REMS, puberty includes those girls who are at least Tanner Stage 3 and have not yet had a menses (premenarchal)
    o For the purpose of this REMS, females who have undergone tubal sterilization are classified as females of reproductive potential
  – Females of non-reproductive potential
    o Pre-pubertal females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential
    o 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
    o 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 the REMS Coordinating Center if she becomes pregnant either while on macitentan or within one month of treatment discontinuation

• Only pharmacies certified in the Macitentan REMS can dispense macitentan to outpatients

• Only inpatient pharmacies that are certified in the Macitentan REMS may stock macitentan for inpatient use

Summary of Macitentan REMS requirements for female patients

All prescribers must be certified in the Macitentan REMS. To become certified, a healthcare provider must complete a Prescriber Enrollment and Agreement Form agreeing to follow the Macitentan REMS requirements. This form must be submitted to the Macitentan REMS online at MacitentanREMSProgram.com or by faxing the completed form to 1-833-681-0003.

All females must be enrolled in the Macitentan REMS in order to receive macitentan. To become enrolled, a patient must complete a Patient Enrollment Form with her prescriber. This form must be submitted to the Macitentan REMS and can be completed online at MacitentanREMSProgram.com or faxing the completed form to the 1-833-681-0003.

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 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 macitentan.
### Prescriber’s role in the Macitentan REMS

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

1. **Read** the macitentan Prescribing Information and this guide to understand the risks of macitentan and to learn about the Macitentan 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 macitentan
5. **Enroll** female patients into the Macitentan REMS by completing a [Patient Enrollment 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 macitentan Prescribing Information and this guide to understand the risks of macitentan and to learn about the Macitentan REMS
   - Prescribers must understand the risks of macitentan and become familiar with the Macitentan REMS

2. **Complete** a [Prescriber Enrollment and Agreement Form](#)
   - You can download the Prescriber Enrollment and Agreement Form from MacitentanREMSProgram.com and fax it to the Macitentan REMS at 1-833-681-0003 or you may certify by enrolling online at MacitentanREMSProgram.com. A completed enrollment form may be printed from the website upon completion of online enrollment.
   - By signing the form, you attest to understanding the risks of macitentan and agree to comply with the Macitentan REMS

3. **Determine** the reproductive potential for female patients
   - Prescribers should identify female patients (captured on the Patient Enrollment Form) as belonging to one of the following categories:
     - Female of reproductive potential (FRP)
     - 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 “Macitentan REMS Overview.”

### Summary of Macitentan REMS requirements for female patients (continued)

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Females of Reproductive Potential</th>
<th>Females of Non-Reproductive Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-pubertal</td>
<td>Post-menopausal or other medical reasons for permanent, irreversible infertility</td>
</tr>
<tr>
<td>Prescriber enrolls female patients into Macitentan REMS</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Prescriber counsels with Guide for Female Patients</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Prescriber must order and review pregnancy tests prior to initiation of treatment, monthly during treatment, and for 1 month after stopping treatment</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Prescriber must verify reproductive status annually in pre-pubertal patients 8 years of age or older by completing the Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Prescriber must complete the Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form upon becoming aware of any change or misclassification in reproductive potential status within 10 business days of awareness</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

* Counsel pre-pubertal female patient and/or parent/guardian.
4. **Educate and counsel** all female patients about the risks of macitentan

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

- 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 macitentan treatment and for one month following treatment discontinuation and emergency contraception using the *Guide for Female Patients*
  - 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 macitentan
  - 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 and receive counseling

- 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 Macitentan REMS by completing the *Patient Enrollment Form*

- Enroll a patient **online**
  - For immediate patient enrollment, please go to MacitentanREMSProgram.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 request to receive an email at the email address entered during enrollment to allow for electronic signature.
  - Print the form and keep it with the patient’s records

- Enroll a patient **by fax** using the printed form
  - Download the *Patient Enrollment Form* from MacitentanREMSProgram.com
  - Confirm patient has agreed to comply with program requirements and has signed the form where indicated
  - Fax the completed form to the REMS Coordinating Center at 1-833-681-0003
  - Keep the original form with the patient’s records

- Ask a patient to **pre-enroll** online to save time at the patient’s office visit
  - Login to MacitentanREMSProgram.com
  - Select the “Send Patient an Invitation to Pre-enroll” button
  - Enter the patient’s name, the patient’s email address, complete the HIPAA acknowledgement, and select the “Send Patient an Invitation to Pre-enroll” button
  - An email will be sent to the patient with a link to allow her to pre-enroll. A pre-enrollment confirmation number will be displayed to the patient upon their completion of pre-enrollment.
  - The patient will be instructed to provide this confirmation number to you.

- Complete a patient enrollment **online** using the patient’s pre-enrollment confirmation number.
  - Login to MacitentanREMSProgram.com
  - Select the “Complete a Patient Enrollment using a Confirmation Number” button
  - Enter the pre-enrollment confirmation number provided by the patient
  - Complete patient enrollment by completing the prescriber portion of the enrollment form
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 macitentan and for one month after stopping treatment
     - Notify the patient and the REMS Coordinating Center if a patient’s pregnancy test is positive
     - Monitor patients’ reproductive status during treatment with macitentan and report any changes or misclassifications to the Macitentan REMS online at [MacitentanREMSProgram.com](http://MacitentanREMSProgram.com) or by completing and submitting the Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form or by contacting the REMS Coordinating Center at 1-888-572-2934 within 10 business days of becoming aware of the change
   - For FNRPs, prescribers must:
     - Monitor patients’ reproductive status during treatment with macitentan and report any changes or misclassifications to the Macitentan REMS online at [MacitentanREMSProgram.com](http://MacitentanREMSProgram.com) or by completing and submitting the Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form or by contacting the REMS Coordinating Center at 1-888-572-2934 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 online or by completing and submitting the Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form or by contacting the REMS Coordinating Center at 1-888-572-2934

---

**Contraceptive options for FRPs**

All FRPs must use reliable contraception during macitentan 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 the REMS Coordinating Center at 1-888-572-2934 of any pregnancies that occur during treatment or within 1 month of discontinuation
Contraceptive options for females of reproductive potential

Acceptable birth control options

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

Certified pharmacies

Due to the risk of serious birth defects, macitentan is only available via certified pharmacies. For a list of certified pharmacies, please visit MacitentanREMSProgram.com or call the REMS Coordinating Center at 1-888-572-2934.

Outpatient Pharmacy Certification:

Only a limited number of certified pharmacies will dispense macitentan for outpatients. Prior to dispensing macitentan to any female, the pharmacy will confirm that the female and the prescriber who wrote the prescription are certified in the Macitentan REMS. A REMS Dispense Authorization (RDA) from the REMS Coordinating Center or the REMS Website must be obtained. If either the female is not enrolled or the prescriber is not certified, or an RDA has not been obtained, macitentan will not be dispensed. Females of reproductive potential and pre-pubertal females will only be able to get a 30-day supply of macitentan at one time. The Medication Guide will be provided to all patients each time macitentan is dispensed. The pharmacy must certify in the Macitentan REMS even if previously certified in the OPSUMIT REMS.

Obtaining a REMS Dispense Authorization

The outpatient pharmacy must obtain an RDA from the Macitentan REMS website or the REMS Coordinating Center. When obtaining an RDA, the outpatient pharmacy must provide the patient’s name, date of birth, and the pharmacy’s NPI number. A new RDA will be issued for each prescription/refill.

If the outpatient pharmacy receives an RDA rejection for the patient, the rejection notification to the pharmacy will indicate which requirements have not been satisfied and that the prescription must not be filled.

If the prescriber is not certified or the patient is not enrolled, a pharmacy associate will contact the prescriber’s office to inform the prescriber of the enrollment and certification requirements.

A pharmacy associate will contact the patient to determine if she has had the monthly pregnancy test. If the patient confirms the monthly pregnancy test, the associate will record the confirmation in the REMS website and attempt to obtain an RDA.

If unable to obtain confirmation from the patient that the pregnancy testing was completed, a pharmacy associate will call the patient’s prescriber to obtain confirmation. If the prescriber confirms that the monthly pregnancy testing has been completed, the pharmacy associate will update the REMS system to indicate the completion of a pregnancy test and attempt to obtain an RDA.

If the prescriber cannot confirm that the pregnancy testing was completed, the pharmacy associate will remind the prescriber of his/her obligation to order and review monthly pregnancy tests and ask the prescriber if he/she authorizes the dispensing of macitentan without confirming the pregnancy test. The patient is eligible to receive macitentan only if the prescriber authorizes the dispensing, the pharmacy associate will update the system to indicate that a pregnancy test has not been completed but the prescriber has authorized the dispensing and attempt to obtain an RDA.
If pregnancy testing confirmation or prescription authorization is not received from the prescriber, the pharmacy may not fill the prescription.

Once the RDA is obtained, the outpatient pharmacy associate must record the NDC number and days’ supply of the dispensed drug in the REMS website or by calling the REMS Coordinating Center. To record this information, the outpatient pharmacy will enter the pharmacy’s NPI Number, the RDA number, the patient’s date of birth, the NDC number, and days supply.

If monthly patient counseling has not been completed at the time the RDA is issued for the female of reproductive potential, the RDA will include a reminder to contact the patient and provide the counseling.

To be certified in the Macitentan REMS, an authorized representative of the outpatient pharmacy must:

• Read the macitentan Prescribing Information and the Prescriber and Pharmacy Guide
• Ensure training of dispensing staff on the Macitentan REMS procedures and materials, including the Prescriber and Pharmacy Guide prior to dispensing macitentan
• Establish processes and procedures to verify the female patient is enrolled, the reproductive status of the patient has not changed, and the prescriber is certified
• Agree to follow the REMS requirements by completing and submitting an Outpatient Pharmacy Enrollment Form to the Macitentan REMS
  – Authorized representatives can complete the Outpatient Pharmacy Enrollment Form:
    • Online at MacitentanREMSProgram.com (a completed enrollment form may be printed from the website)
    • By faxing the printed form to 1-833-681-0003

Prior to dispensing, the outpatient pharmacy must:

• Obtain a REMS Dispense Authorization (RDA) from the REMS Coordinating Center or the REMS website that verifies female patients are enrolled, the reproductive status has not changed, the prescriber is certified, and pregnancy test is completed for females of reproductive potential or the prescriber authorizes the dispensing.
• Not fill the prescription if an RDA cannot be obtained.
• For all female patients, record the NDC number and days’ supply of the dispensed drug with the REMS once an RDA is obtained.

To maintain certification to dispense, the outpatient pharmacy must:

• Re-certify in the Macitentan REMS if the outpatient pharmacy designates a new authorized representative by completing, signing, and submitting a new Outpatient Pharmacy Enrollment Form as soon as the designated authorized representative changes.

At all times, the outpatient pharmacy must:

• Notify the REMS Coordinating Center or FDA if any patient becomes pregnant during macitentan treatment
• Not distribute, transfer, loan, or sell macitentan, except to certified dispensers
• For females of reproductive potential: Maintain and submit records of daily product dispensing data
• Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed

Females of reproductive potential will be contacted each month by the pharmacy to arrange dispensing of macitentan. The pharmacy will:

• Ask if she has had a pregnancy test within the last month or verify that the prescriber authorizes the dispensing through the processes and procedures established as a requirement of the REMS.
• Counsel her on the need to use reliable contraception during macitentan 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
• Dispense no more than a 30-days’ supply.
• Maintain and submit records of daily product dispensing data.

For pre-pubertal females, outpatient pharmacies will:

• Counsel her to inform her prescriber immediately if her reproductive status changes
• Dispense no more than a 30-days’ supply.

Note: If monthly counseling has not been completed when an RDA is issued, the RDA will include a reminder for the pharmacy to contact the patient and provide counseling.

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 Macitentan REMS.
• Dispense to a female patient only after she has been enrolled in the Macitentan 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 macitentan in the outpatient setting until such time that enrollment has been completed.
• Dispense no more than a fifteen- (15-) day temporary supply of macitentan upon discharge of any patient.
• Not distribute, transfer, loan, or sell macitentan, except to dispensers certified in the Macitentan REMS.
To be certified in the Macitentan REMS, an authorized representative of the inpatient pharmacy must:

- Read the macitentan Prescribing Information and the Prescriber and Pharmacy Guide
- Put processes and procedures in place to ensure the Macitentan REMS requirements are met
- Ensure training of dispensing staff on the Macitentan REMS procedures and materials, including the Prescriber and Pharmacy Guide prior to dispensing macitentan
- Agree to follow the REMS requirements by completing an Inpatient Pharmacy Enrollment Form online or submitting a completed form via fax to the Macitentan REMS Coordinating Center at 1-833-681-0003.

Authorized representatives can complete the Inpatient Pharmacy Enrollment Form:

- Online at MacitentanREMSProgram.com (a completed enrollment form may be printed from the website)
- By fax at 1-833-681-0003

To maintain certification to dispense, the inpatient pharmacy must:

- Re-certify by enrolling in the Macitentan 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.

At all times, the inpatient pharmacy must:

- Notify the Macitentan REMS at 1-888-572-2934 or FDA if any patient becomes pregnant during macitentan treatment
- Develop a process to track compliance with the conditions above and provide information about its compliance to the Macitentan REMS
- Agree that this pharmacy may be audited by the FDA, the Macitentan REMS, or a designated third party

How can an inpatient pharmacy verify a patient enrollment and prescriber certification before dispensing?

Before dispensing to a female inpatient, the inpatient pharmacy must verify that the patient is under the supervision and care of a certified prescriber, and that she is enrolled or will be enrolled in the Macitentan REMS prior to discharge. This may be verified online at MacitentanREMSProgram.com or by phone by calling the REMS Coordinating Center.

If an inpatient pharmacy needs macitentan and is not certified in the Macitentan REMS, please go to MacitentanREMSProgram.com for immediate online enrollment and certification or contact the REMS Coordinating Center, Monday through Friday 8:00 AM to 8:00 PM ET, at 1-888-572-2934 for assistance in enrolling.

To learn more about the serious risks associated with macitentan, 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 MacitentanREMSProgram.com.
You can reach the Macitentan REMS by calling toll free at 1-888-572-2934.

Monday – Friday
8:00 AM – 8:00 PM ET

For more information about the Macitentan REMS, please visit MacitentanREMSProgram.com