I. Administrative Information

Initial Shared System REMS Approval: [XX/YYYY]

II. REMS Goal

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

III. REMS Requirements

Macitentan Applicants must ensure that healthcare providers, patients, pharmacies, and wholesalers-distributors comply with the following requirements:

1. Healthcare Providers who prescribe macitentan must:

   To become certified to prescribe

   1. Review the drug’s Prescribing Information.

   2. Review the following: Prescriber and Pharmacy Guide.

   3. Enroll in the REMS by completing the Prescriber Enrollment Form and submitting it to the REMS Program.

Before treatment initiation (first dose)

4. For all females: Assess the patient’s reproductive status using the definitions in the Prescriber and Pharmacy Guide. Document and submit the results to the REMS Program using the Patient Enrollment Form.

5. For all females: Counsel the patient that the drug is only available through a restricted distribution program.
6. For females of reproductive potential: Assess the patient’s pregnancy status by ordering and reviewing her pregnancy test result.

7. For females of reproductive potential: Counsel the patient on the risk of embryo-fetal toxicity, the need to use reliable contraception during treatment and for one month following treatment discontinuation, and emergency contraception using the Guide for Female Patients.

8. For pre-pubertal females: Counsel the patient on the risk of embryo-fetal toxicity and to immediately contact her prescriber if she begins to menstruate using the Guide for Female Patients.

9. Enroll all female patients by completing and submitting the Patient Enrollment Form and submitting it to the REMS Program.

10. For females of reproductive potential: Counsel the patient if she is not complying with required testing, if she is not using appropriate contraception, and to contact her prescriber if she misses a menstrual period or suspects that she is pregnant.

11. For females of reproductive potential: Assess the patient’s pregnancy status by ordering and reviewing her pregnancy test result.

12. For pre-pubertal females at least age 8 years or older: Document reproductive potential status and submit to the REMS Program using the Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form.

13. For females of reproductive potential: Assess the patient’s pregnancy status by ordering and reviewing her pregnancy test result.

14. For pre-pubertal females: Assess the patient’s reproductive status.

15. Report pregnancies to the REMS Coordinating Center.

16. Report a change or misclassification in reproductive status to the REMS Program using the Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form.

2. Females of reproductive potential who are prescribed macitentan:

Before treatment initiation

1. Review the Guide for Female Patients.

2. Get a pregnancy test.
3. Enroll in the REMS by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS Program.

4. Receive counseling from the prescriber on the risk of embryo-fetal toxicity, the need to use reliable contraception, and emergency contraception using the Guide for Female Patients.

5. Adhere to the safe use condition: Communicate with the pharmacy to confirm completion of pregnancy testing.

| During treatment; before each dispensing | 6. Receive counseling from the pharmacy on the risk of embryo-fetal toxicity, the need for reliable contraception during treatment and for one month after stopping treatment, to get monthly pregnancy tests, and to immediately contact her prescriber if she misses a menstrual period or suspects she is pregnant. |
| During treatment and after treatment discontinuation for one month | 9. Adhere to the safe use condition: Use reliable contraception as described in the Guide for Female Patients. |
| After treatment discontinuation; one month | 11. Get a pregnancy test. |
| At all times | 12. Inform the prescriber immediately if you miss a menstrual period or suspect a pregnancy. |

### 3. Pre-pubertal females who are prescribed macitentan:

| Before treatment initiation | 1. Review the Guide for Female Patients. |
| 2. Enroll in the REMS Program by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS Program. |
| 3. Receive counseling from the prescriber on the risk of embryo-fetal toxicity and to contact your prescriber if you begin to menstruate using the Guide for Female Patients. |

| At all times | 4. If over the age of 8: Be monitored for a change in reproductive status. |
5. Inform the prescriber if there is a change in reproductive status.

### 4. Post-menopausal females or females with other medical reason for permanent, irreversible infertility who are prescribed macitentan:

<table>
<thead>
<tr>
<th>Before treatment initiation</th>
<th>1. Review the Guide for Female Patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Enroll in the REMS Program by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS Program.</td>
</tr>
</tbody>
</table>

| At all times | 3. Inform the prescriber if there is a change in your reproductive status. |

### 5. Outpatient Pharmacies that dispense macitentan must:

<table>
<thead>
<tr>
<th>To become certified to dispense</th>
<th>1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the outpatient pharmacy.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Have the authorized representative review the Prescribing Information and the Prescriber and Pharmacy Guide.</td>
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<tr>
<td></td>
<td>3. Have the authorized representative enroll in the REMS Program by completing the Outpatient Pharmacy Enrollment Form and submitting it to the REMS Program.</td>
</tr>
<tr>
<td></td>
<td>4. Train all relevant staff involved in dispensing on the Macitentan REMS requirements, procedures, and REMS materials.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Before dispensing</th>
<th>5. Obtain authorization to dispense each prescription by contacting the REMS Program to verify 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 refill.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6. For females of reproductive potential: Counsel the patient on the risk of embryo-fetal toxicity, the need to use reliable contraception during treatment and for one month after stopping treatment, to get monthly pregnancy tests, and to inform the prescriber immediately if she misses a menstrual period or suspects she is pregnant.</td>
</tr>
<tr>
<td></td>
<td>7. For females of reproductive potential: Dispense no more than a 30-days' supply.</td>
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</tbody>
</table>

| To maintain certification to dispense | 8. Have a new authorized representative enroll in the REMS Program by completing the Outpatient Pharmacy Enrollment Form if the authorized representative changes. |

| At all times | 9. Report pregnancies to the REMS Coordinating Center. |
10. Not distribute, transfer, loan, or sell macitentan, except to certified dispensers.

11. For all females: Maintain and submit records of daily product dispensing data.

12. Maintain records that all processes and procedures are in place and are being followed.

13. 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.

### 6. Inpatient Pharmacies that dispense macitentan must:

<table>
<thead>
<tr>
<th>To become certified to dispense</th>
<th>1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Have the authorized representative review the Prescribing Information and the <a href="#">Prescriber and Pharmacy Guide</a>.</td>
</tr>
<tr>
<td></td>
<td>3. Have the authorized representative enroll in the REMS Program by completing the <a href="#">Inpatient Pharmacy Enrollment Form</a> and submitting it to the REMS Program.</td>
</tr>
<tr>
<td></td>
<td>4. Train all relevant staff involved in dispensing macitentan on the REMS Program requirements, procedures, and REMS materials.</td>
</tr>
<tr>
<td></td>
<td>5. Establish processes and procedures to verify the female patient is enrolled in the REMS program or will be enrolled prior to discharge, her reproductive status, and the female patient is under the supervision and care of a certified prescriber.</td>
</tr>
<tr>
<td></td>
<td>6. For females of reproductive potential: establish processes and procedures to verify pregnancy testing is complete, and that the patient is counseled on the risk of embryo-fetal toxicity, the need to use reliable contraception, to get monthly pregnancy tests, and to inform the prescriber of a pregnancy immediately.</td>
</tr>
<tr>
<td>Before dispensing</td>
<td>7. Verify the female patient is under the supervision and care of a certified prescriber, and that she is enrolled or will be enrolled in the REMS Program prior to discharge through the processes and procedures established as a requirement of the REMS Program.</td>
</tr>
<tr>
<td></td>
<td>8. For females of reproductive potential: Verify the pregnancy testing is complete, and that the patient is counseled on the risk of embryo-fetal toxicity, the need to use reliable contraception, to get monthly pregnancy tests, and to inform the prescriber of a pregnancy immediately through the processes and procedures established as a requirement of the REMS Program.</td>
</tr>
</tbody>
</table>
To maintain certification to dispense

9. Have a new authorized representative enroll in the REMS Program by completing the Inpatient Pharmacy Enrollment Form if the authorized representative changes.

At discharge

10. Dispense no more than a 15-days’ supply.

At all times

11. Report pregnancies to the REMS Coordinating Center.

12. Not distribute, transfer, loan, or sell macitentan, except to certified dispensers.

13. Maintain records that all processes and procedures are in place and are being followed.

14. Comply with audits carried out by the manufacturer or a third party acting on behalf of the manufacturer to ensure that all processes and procedures are in place and are being followed.

7. **Wholesalers-distributors that distribute macitentan must:**

<table>
<thead>
<tr>
<th>To be able to distribute</th>
<th>1. Establish processes and procedures to ensure that the drug is distributed only to certified pharmacies.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>2. Train all relevant staff involved in distribution on the Macitentan REMS requirement.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>At all times</th>
<th>3. Distribute only to certified pharmacies.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>4. Maintain and submit records of monthly drug distribution for all macitentan shipments.</td>
</tr>
<tr>
<td></td>
<td>5. 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.</td>
</tr>
</tbody>
</table>

**Macitentan Applicants must provide training to healthcare providers who prescribe macitentan.**
The training includes the following educational materials: Prescribing Information and Prescriber and Pharmacy Guide. The training must be available online or by calling the REMS Program.

**Macitentan must provide training to pharmacies that dispense macitentan.**
The training includes the following educational material: Prescribing Information and Prescriber and Pharmacy Guide. The training must be available online or by calling the REMS Program.

**To support REMS Program operations, Macitentan Applicants must:**

1. Establish and maintain a REMS Program website, [www.MacitentanREMSProgram.com](http://www.MacitentanREMSProgram.com). The REMS Program website must include the capability to complete prescriber and pharmacy enrollment online, the capability to enroll and manage patients online, including obtaining patient authorization status,
and the option to print the Prescribing Information, Medication Guide, and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program website. The REMS Program website must not link back to the promotional product website.

2. Make the REMS Program website fully operational and all REMS materials available through the REMS Program website or REMS Coordinating Center within 60 calendar days of when the first abbreviated new drug application (ANDA) joining a shared system REMS with Opsumit (macitentan) is approved.

3. Establish and maintain a REMS Coordinating Center for REMS participants at 1-888-572-2934.

4. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the Macitentan REMS.

5. Ensure prescribers and pharmacies are able to complete the certification process online and by fax.

6. Ensure prescribers are able to report change in reproductive status online and by fax.

7. Ensure prescribers are able to complete the patient enrollment process online and by fax.

8. Ensure outpatient pharmacies are able to obtain authorization before dispensing by phone and online. The authorization must include the patient’s counseling status. The authorization number is valid for 5 calendar days after the expected refill date.

9. Ensure inpatient pharmacies are able to verify patient enrollment status and prescriber certification by phone and online.

10. Ensure prescribers are able to confirm pregnancy testing by phone and online.

11. Ensure the REMS Coordinating Center contacts the prescriber of a pre-pubertal female annually to have the prescriber verify the pre-pubertal female’s reproductive status by completing the Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form.

12. Ensure the REMS Coordinating Center updates the database and notifies certified pharmacies of patient’s change in reproductive status within one business day of receipt of a completed Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form.

13. Ensure pharmacies are able to enroll as inpatient (including, but not limited to, pharmacies in hospitals, long-term care facilities, prisons, and state psychiatric units) or as outpatient pharmacies.

14. Provide the Prescriber Enrollment Form and Prescriber and Pharmacy Guide to prescribers who (1) attempt to prescribe macitentan and are not yet certified or (2) inquire about how to become certified.

15. Provide certified prescribers access to the database of certified pharmacies and enrolled patients.

16. Provide certified pharmacies access to the database of certified prescribers and enrolled patients.

17. Provide registered wholesalers-distributors access to the database of certified pharmacies.

To ensure REMS participants’ compliance with the REMS Program, Macitentan Applicants must:

18. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: macitentan distribution and dispensing; certification of prescribers and pharmacies; enrolled patients; and audits of REMS pharmacies and wholesalers-distributors. These records must be readily available for FDA inspections.

19. Establish a plan for addressing noncompliance with REMS Program requirements.

20. Monitor prescribers, pharmacies, and wholesaler-distributors on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if noncompliance is identified, including de-certification.

21. Audit all certified outpatient pharmacies and wholesaler-distributors within 180 days after they become certified, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.

22. Audit all certified outpatient pharmacies, all wholesaler-distributors, the coordinating center for macitentan, and at least 10% or at least 20 whichever is greater of certified inpatient pharmacies that have ordered macitentan annually to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.
23. Take reasonable steps to improve operation of and compliance with the requirements in the Macitentan REMS based on monitoring and evaluation of the Macitentan REMS.

**IV. REMS Assessment Timetable**

Macitentan NDA Applicants must submit REMS Assessments at 1 year from the date of the initial Shared System REMS approval [MM/DD/YYYY], 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 calendar days before the submission date for that assessment. Macitentan NDA Applicants must submit each assessment so that it will be received by the FDA on or before the due date.

**V. REMS Materials**

The following materials are part of the Macitentan REMS:

**Enrollment Forms**
- Prescriber:
  1. Prescriber Enrollment and Agreement Form
- Patient:
  2. Patient Enrollment Form
  3. Patient Enrollment Form for VA use only
- Pharmacy:
  4. Inpatient Pharmacy Enrollment Form
  5. Outpatient Pharmacy Enrollment Form

**Training and Educational Materials**
- Prescriber:
  6. Prescriber and Pharmacy Guide
- Patient:
  7. Guide for Female Patients
- Pharmacy:
  8. Prescriber and Pharmacy Guide

**Patient Care Form**
- 9. Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form

**Other Materials**
- 10. REMS Program website (www.MacitentanREMSProgram.com)