

A. Ambrisentan Shared System REMS Program

I. Administrative Information

Initial Shared System REMS Approval: 03/2019

II. REMS Goal

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

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

III. REMS Requirements

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

1. Healthcare Providers who prescribe ambrisentan 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.
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Before treatment

4. For all females: Assess the patient's reproductive status using the definitions
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initiation (first dose)	<p>in the Prescriber and Pharmacy Guide. Document and submit the results to the REMS Program using the Patient Enrollment Form.</p> <p>5. For all females: Counsel the patient that the drug is only available through a restricted distribution program.</p> <p>6. For females of reproductive potential: Counsel the patient on the risk of embryo-fetal toxicity, the need to use highly reliable contraception during treatment and for one month following treatment discontinuation, and emergency contraception using the Guide for Female Patients.</p> <p>7. For females of reproductive potential: Assess the patient's pregnancy status by ordering and reviewing her pregnancy test result.</p> <p>8. For pre-pubertal females: Counsel the patient on the risk of embryo-fetal toxicity using the Guide for Female Patients.</p> <p>9. Enroll all female patients by completing the Patient Enrollment Form and submitting it to the REMS Program.</p>
During treatment; before each prescription	<p>10. For females of reproductive potential: Counsel the patient if she is not complying with the required testing or if she is not using appropriate contraception.</p> <p>11. For females of reproductive potential: Assess the patient's pregnancy status by ordering and reviewing her pregnancy test result.</p>
During treatment; at least annually	<p>12. For pre-pubertal females at least age 8 or older: Document reproductive status and submit to the REMS Program using Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form.</p>
After treatment discontinuation; for one month	<p>13. For females of reproductive potential: Assess the patient's pregnancy status by ordering and reviewing her pregnancy test result.</p>
At all times	<p>14. For pre-pubertal females: Assess the patient's reproductive status.</p> <p>15. Report pregnancies to the REMS Program.</p>
At all times, within 10 business days	<p>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.</p>

2. Females of reproductive potential who are prescribed ambrisentan:

Before treatment initiation	<ol style="list-style-type: none">1. Review the Guide for Female Patients.2. Get a pregnancy test.3. Enroll in the REMS Program 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 and the need to use highly reliable contraception during treatment and for one month following treatment discontinuation, and emergency contraception using the Guide for Female Patients.
During treatment; before dispensing	<ol style="list-style-type: none">5. Receive counseling from the pharmacy or healthcare provider who dispenses ambrisentan on the risk of embryo-fetal toxicity, the need to use highly reliable contraception during treatment and for one month following treatment discontinuation, emergency contraception, to get monthly pregnancy tests, and to report a pregnancy immediately.6. Get a pregnancy test.7. Adhere to the safe use condition: Communicate with the pharmacy to confirm completion of pregnancy testing.
During treatment and after treatment discontinuation for one month	<ol style="list-style-type: none">8. Adhere to the safe use condition: Use highly reliable contraception as described in the Guide for Female Patients.
After treatment discontinuation; one month	<ol style="list-style-type: none">9. Get a pregnancy test.

3. Pre-pubertal females who are prescribed ambrisentan:

Before treatment initiation	<ol style="list-style-type: none">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 using the Guide for Female Patients.
At all times	<ol style="list-style-type: none">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 your reproductive status.

4. Post-menopausal females or females with other medical reasons for permanent, irreversible infertility who are prescribed ambrisentan:

Before treatment initiation	<ol style="list-style-type: none">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.
At all times	<ol style="list-style-type: none">3. Inform the prescriber if there is a change in your reproductive status.

5. Outpatient pharmacies and healthcare providers that dispense ambrisentan must:

To become certified to dispense	<ol style="list-style-type: none">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.2. Have the authorized representative review the Prescriber and Pharmacy Guide.3. Have the authorized representative enroll in the REMS Program by completing the Outpatient Pharmacy Enrollment Form and submitting it to the REMS Program.4. Train all relevant staff involved in dispensing ambrisentan on the REMS Program requirements using the Prescriber and Pharmacy Guide.5. 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.6. For females of reproductive potential: Establish processes and procedures to verify that pregnancy testing is complete or the prescriber authorizes the refill.
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| Before dispensing | <ol style="list-style-type: none">7. For females of reproductive potential: Counsel the patient on the risk of embryo-fetal toxicity, the need to use highly reliable contraception during treatment and for one month following treatment discontinuation, emergency contraception, to get monthly pregnancy tests, and inform the prescriber of a pregnancy immediately.8. Verify the female patient is enrolled, the reproductive status has not changed, and the prescriber is certified through the processes and procedures established as a requirement of the REMS Program.9. For females of reproductive potential: Verify that the pregnancy testing is complete or the prescriber authorizes the refill through the processes and procedures established as a requirement of the REMS Program.10. For females of reproductive potential: Dispense no more than a 30 days' supply. |
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| At all times | <ol style="list-style-type: none">11. Report pregnancies to the REMS Program.12. Report a change or misclassification in reproductive status to the REMS Program.13. Not distribute, transfer, loan, or sell ambrisentan, except to certified dispensers.14. For females of reproductive potential: Maintain and submit records of daily product dispensing data.15. Maintain records that all processes and procedures are in place and are being followed.16. 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. |
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6. Inpatient pharmacies that dispense ambrisentan must:

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| To become certified to dispense | <ol style="list-style-type: none">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.2. Have the authorized representative review the Prescriber and Pharmacy Guide.3. Have the authorized representative enroll in the REMS Program by completing Inpatient Pharmacy Enrollment Form and submitting it to the REMS Program.4. Train all relevant staff involved in dispensing ambrisentan on the REMS Program requirements using the Prescriber and Pharmacy Guide.5. Establish processes and procedures to verify the female patient is enrolled or will be enrolled in the REMS Program prior to discharge, her reproductive |
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status, and the female patient is under the supervision and care of a certified prescriber.

6. For females of reproductive potential: Establish processes and procedures to verify pregnancy testing is complete, the patient is counseled on the risk of embryo-fetal toxicity, the need to use highly reliable contraception during treatment and for one month following treatment discontinuation, to get monthly pregnancy tests, and to inform the prescriber of a pregnancy immediately.

Before dispensing

7. Verify the female patient is under the supervision and care of a certified prescriber, her reproductive status, 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.
8. For females of reproductive potential: Verify that pregnancy testing is complete, the patient is counseled on the risk of embryo-fetal toxicity, the need to use highly reliable contraception during treatment and for one month after stopping treatment, 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.

At discharge

9. Dispense no more than a 15 days' supply.

At all times

10. Report pregnancies to the REMS Program.
11. Report a change or misclassification in reproductive status to the REMS Program.
12. Not distribute, transfer, loan, or sell ambrisentan, 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 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.

7. Wholesalers-distributors that distribute ambrisentan must:

To be able to distribute

1. Establish processes and procedures to ensure that the drug is distributed only to certified pharmacies.
 2. Train all relevant staff involved in distribution on the REMS Program requirements.
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At all times

1. Distribute only to certified pharmacies.
 2. Maintain records of drug distribution.
 3. 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.
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Ambrisentan Applicants must provide training to healthcare providers who prescribe ambrisentan.

The training includes the following educational material: [Prescriber and Pharmacy Guide](#). The Training must be available online and hard copy format via mail or fax.

Ambrisentan Applicants must provide training to pharmacies that dispense ambrisentan.

The training includes the following educational material: [Prescriber and Pharmacy Guide](#). The Training must be available online and hard copy format via mail or fax.

To support REMS Program operations, Ambrisentan Applicants must:

1. Establish and maintain a REMS Program website, www.ambrisentanrems.us.com. The REMS Program website must include the capability to complete prescriber and inpatient pharmacy certification or enrollment online, the capability to enroll and manage patients online, 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(s).
2. Make the REMS Program website fully operational and all REMS materials available through website and REMS coordinating center prior to the marketing of any ambrisentan product covered by this REMS that was approved under an ANDA.
3. Establish and maintain a REMS coordinating center for REMS participants at 1-888-417-3172.
4. Establish and maintain a validated, secure database of all REMS participants who are enrolled and certified in the REMS Program.
5. Ensure prescribers and inpatient pharmacies are able to complete the certification process by fax and online.
6. Ensure outpatient pharmacies are able to complete the certification process by fax.
7. Ensure prescribers are able to report change in reproductive status by fax and online.
8. Ensure prescribers are able to complete the patient enrollment process by fax and online.
9. Ensure pharmacies are able to confirm patient enrollment and prescriber certification before dispensing by phone and online.
10. Ensure that 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](#).
11. Ensure the REMS coordinating center updates the database and notifies certified pharmacies of a 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](#).
12. 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 outpatient pharmacies.
13. Notify prescribers and pharmacies within one business day after they become certified in the REMS Program.
14. Provide certified prescribers access to the database of certified pharmacies and enrolled patients.

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

To ensure REMS participants' compliance with the REMS Program, Ambrisentan Applicants must:

16. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: ambrisentan distribution and dispensing; certification of prescribers, pharmacies; enrolled patients; and audits of REMS participants. These records must be readily available for FDA inspections.
17. Establish a plan for addressing noncompliance with REMS Program requirements.
18. Monitor prescribers, pharmacies, and wholesaler-distributors on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.
19. Audit all certified outpatient pharmacies, registered wholesalers-distributors and the REMS coordinating center within 180 calendar days of being certified/registered in the REMS and annually to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements, and include risk-based auditing of inpatient pharmacies annually.
20. Take reasonable steps to improve implementation of and compliance with the requirements in the REMS Program based on monitoring and evaluation of the REMS Program.

IV. REMS Assessment Timetable

Ambrisentan NDA Applicants must submit REMS Assessments annually from the date of the initial REMS approval (03/28/2019). 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. Ambrisentan 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 Ambrisentan REMS:

Enrollment Forms

Prescriber:

1. [Prescriber Enrollment and Agreement Form](#)

Patient:

2. [Patient Enrollment and Consent Form](#)

Pharmacy:

3. [Outpatient Pharmacy Enrollment Form](#)
4. [Inpatient Pharmacy Enrollment Form](#)

Training and Educational Materials

Prescriber:

5. [Prescriber and Pharmacy Guide](#)

Patient:

6. [Guide for Female Patients](#)

Pharmacy:

7. [Prescriber and Pharmacy Guide](#)

Patient Care Form

8. [Change in Reproductive Status and Pre-Pubertal Annual Verification Form](#)

Other Materials

9. [REMS Program website \(www.ambrisentanrems.us.com\)](http://www.ambrisentanrems.us.com)