

AMBRISENTAN RISK EVALUATION
AND MITIGATION STRATEGY (REMS)

Ambrisentan REMS
**PRESCRIBER AND
PHARMACY GUIDE**

This guide is part of an FDA-approved REMS.

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Ambrisentan REMS

Indication

Ambrisentan is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and delay clinical worsening.

Studies establishing effectiveness included trials predominantly in patients with WHO Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).

Risk of embryo-fetal toxicity

Ambrisentan may cause fetal harm when administered to a pregnant female and is contraindicated during pregnancy. There is limited data on ambrisentan use in pregnant females; the possibility of serious birth defects in humans cannot be excluded.

Pregnancy must be excluded prior to the initiation of ambrisentan treatment, monthly thereafter, and for one month following treatment discontinuation.

Ambrisentan REMS

Because of the risk of serious birth defects, ambrisentan is only available to females through a restricted distribution program under an FDA-required REMS. The goal of the Ambrisentan REMS is to mitigate the risk of embryo-fetal toxicity associated with ambrisentan by:

- Ensuring prescribers are educated on the following:
 - the risks of embryo-fetal toxicity
- 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 Ambrisentan REMS
 - monitoring patients at baseline and monthly
- Ensuring that pharmacies are educated on the following:
 - the risks of embryo-fetal toxicity
- Ensuring that pharmacies are educated on and adhere to the following:
 - confirming that the appropriate patient monitoring and counseling has occurred before dispensing ambrisentan
- Ensuring that patients are informed about:
 - the risks of embryo-fetal toxicity
 - appropriate baseline and monthly patient monitoring
 - appropriate contraception

Overview of the Ambrisentan REMS

- Ambrisentan is only available to females through a restricted distribution program
- Prescribers must enroll in the Ambrisentan REMS and comply with the Ambrisentan REMS requirements to prescribe ambrisentan
- All female patients must enroll in the Ambrisentan REMS to receive ambrisentan
- Prescribers must educate and counsel Females of Reproductive Potential and Pre-Pubertal Females on the risks of ambrisentan, including the risk of serious birth defects using the *Guide for Female Patients*. The parent/guardian of the Pre-Pubertal Female must also be educated and counseled on the risks of ambrisentan
- Prescribers must order and review pregnancy tests for Females of Reproductive Potential prior to initiation of treatment, monthly during treatment, and for one month following treatment discontinuation

Requirement	Female of Reproductive Potential	Female of Non-Reproductive Potential		
		Pre-Pubertal	Post-Menopausal	Other medical reasons for permanent, irreversible infertility
Prescriber enrolls female patients into Ambrisentan REMS	X	X	X	X
Review <i>Guide for Female Patients</i>	X	X	X	X
Counseling with <i>Guide for Female Patients</i>	X	X		
Prescriber must order and review pregnancy tests prior to initiation of treatment, monthly during treatment, and for one month following treatment discontinuation	X			
Prescriber must verify reproductive status annually by completing the <i>Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form</i> for females who are at least 8 years of age and older		X		
Prescriber must complete the <i>Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form</i> upon becoming aware of any change in reproductive status within 10 business days of awareness	X	X	X	X

Role of Prescriber in the Ambrisentan REMS

Prescribers must complete the following steps in the Ambrisentan REMS:

1. Read the Ambrisentan Prescribing Information and this guide to understand the Ambrisentan REMS and the risks of ambrisentan

2. Complete the *Prescriber Enrollment Form*

- You will attest to understanding the risks of ambrisentan and agree to comply with the requirements of the Ambrisentan REMS
- Complete the form online at www.ambrisentanrems.us.com or fax the completed form to 1-866-750-9802

3. Determine the reproductive status of female patients

Females of Reproductive Potential:

- Females of Reproductive Potential include girls who have entered puberty and all women 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 Females:** Females who have passed through Menopause (as defined below)
- **Females with other medical reasons for permanent, irreversible infertility**

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 from bilateral oophorectomy

4. Educate/counsel all female patients about the risks of ambrisentan and about the Ambrisentan REMS

- Advise all females that ambrisentan is only available through a restricted distribution program called the Ambrisentan REMS

For Females of Reproductive Potential:

- Review the **Guide for Female Patients** prior to initiating treatment
- Counsel the patient about the risk of embryo-fetal toxicity, the need to use highly reliable contraception (see page 6) during ambrisentan treatment and for one month following treatment discontinuation, and the need to use emergency contraception using the **Guide for Female Patients**
- Assess the patient's pregnancy status by ordering and reviewing pregnancy tests prior to initiation of ambrisentan treatment, monthly during treatment, and for one month following treatment discontinuation
- Advise the patient of the requirement for monthly pregnancy tests to confirm they are not pregnant so they can receive ambrisentan
- Counsel if she is not complying with the required testing of if she is not using appropriate contraception
- Submit a **Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form** within 10 business days of becoming aware of any change in reproductive status
- Prescribe no more than a 30 days' supply at a time
- Notify the Ambrisentan REMS if any patient becomes pregnant during ambrisentan treatment or within one month following treatment discontinuation

For Females of Non-Reproductive Potential:

For Pre-Pubertal Females:

- Review the **Guide for Female Patients** prior to initiating treatment
- Counsel the patient and parent/guardian about the risk of embryo-fetal toxicity using the **Guide for Female Patients**
- Evaluate regularly for any changes in reproductive status while receiving ambrisentan
- Verify the reproductive status annually for Pre-Pubertal Females who are at least 8 years of age and older by completing and submitting the **Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form**
- Report a change or misclassification in reproductive status by completing and submitting the **Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form** within 10 business days of becoming aware of the change
- Notify the Ambrisentan REMS if any patient becomes pregnant during ambrisentan treatment or within one month following treatment discontinuation

For Post-Menopausal Females:

- Review the **Guide for Female Patients** prior to initiating treatment
- Report a change or misclassification in reproductive status by completing and submitting the **Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form** within 10 business days of becoming aware

For females with other medical reasons for permanent, irreversible infertility:

- Review the **Guide for Female Patients** prior to initiating treatment
- Report a change or misclassification in reproductive status by completing and submitting the **Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form** within 10 business days of becoming aware

5. Check pregnancy status in Female of Reproductive Potential

- Order and review pregnancy test results for the patient:
 - Prior to initiating treatment
 - Monthly during treatment
 - One month following treatment discontinuation

The patient must agree to be contacted by the certified pharmacy prior to each shipment to confirm that a pregnancy test was completed, and she must also agree to be contacted by the Ambrisentan REMS if she becomes pregnant while on ambrisentan or within one month of stopping treatment.

6. Enroll all female patients into the Ambrisentan REMS

- Complete and submit the **Patient Enrollment Form** via fax to 1-866-750-9802 or login to complete and submit online at www.ambrisentanrems.us.com.
- Keep the original form with the patient's records

7. Evaluate reproductive status of female patients throughout treatment

- Report a change or misclassification in reproductive status to the Ambrisentan REMS within 10 business days of becoming aware of the change by faxing the completed **Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form** to 1-866-750-9802 or online at www.ambrisentanrems.us.com. Verify the reproductive status of Pre-Pubertal Females who are at least 8 years of age or older annually by completing and submitting the **Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form**
- Counsel females who fail to comply with the Ambrisentan REMS requirements
- Notify the Ambrisentan REMS if any patient becomes pregnant during ambrisentan treatment or within one month following treatment discontinuation

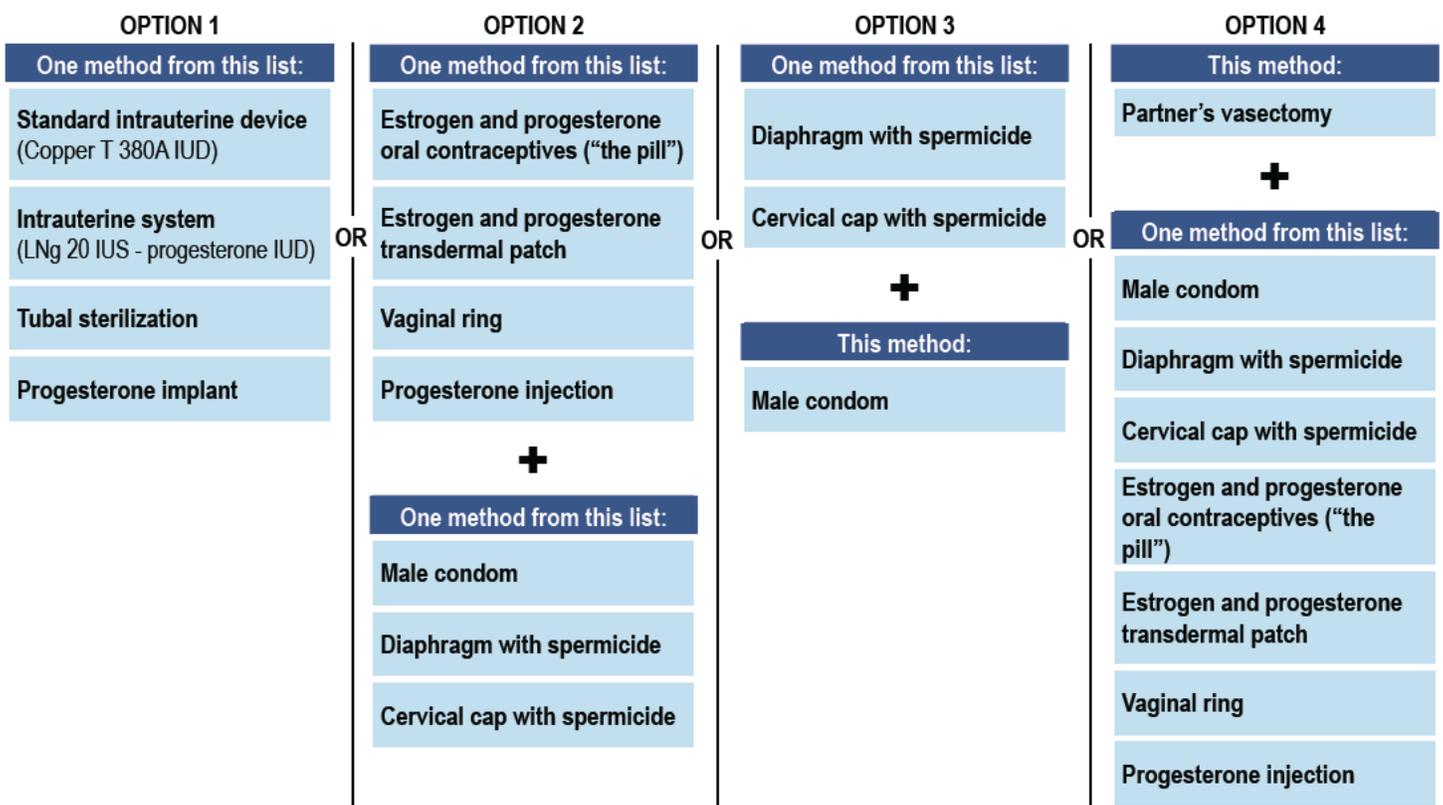
Contraceptive Options for Females of Reproductive Potential

All Females of Reproductive Potential should undergo contraceptive counseling with either the prescriber or another designated healthcare practitioner trained in contraceptive counseling.

Please refer to the diagram below for a complete list of the acceptable contraceptive options. The same diagram also appears in the *Guide for Female Patients* and should be used to discuss acceptable birth control options with patients.

- Educate and counsel Females of Reproductive Potential on the use of emergency contraception in the event of unprotected sex or known or suspected contraceptive failure
- Remind patients to report to you immediately any delay in having a period or any other reason of suspected pregnancy during treatment
- If pregnancy is suspected for any reason, a pregnancy test must be performed
- **The prescriber must notify the Ambrisentan REMS of any pregnancies that occur during treatment or within one month following treatment discontinuation**

Contraceptive Options for Females of Reproductive Potential



Role of Certified Pharmacies

Outpatient Pharmacy Dispensing:

Only a limited number of certified pharmacies will dispense ambrisentan for outpatients. In order for patients to receive ambrisentan, all outpatient pharmacies that wish to stock this product, must enroll in the Ambrisentan REMS and agree to comply with the requirements of the program.

Prior to dispensing, the outpatient pharmacy must:

- For Females of Reproductive Potential: Counsel the patient on the risk of embryo-fetal toxicity, the need to use highly reliable contraception and emergency contraception, to get monthly pregnancy tests, and to inform the prescriber of a pregnancy immediately.
- Verify with the Ambrisentan REMS that the patient's prescriber is enrolled for all patients and if the patient is female, verify the patient is enrolled and the reproductive status has not changed.
- For Females of Reproductive Potential: Verify that the pregnancy testing is complete or the prescriber authorizes the refill.
- For Females of Reproductive Potential: Dispense no more than a 30 days' supply
 - A certified prescriber may be eligible to provide the outpatient pharmacy a one time authorization to dispense a greater than 30 day supply for a FRP and the outpatient pharmacy must report the reason to the Ambrisentan REMS for approval. For information on the eligibility to dispense more than a 30 day supply and related authorization process, contact the Ambrisentan REMS at 1-888-417-3172.

At all times, the outpatient pharmacy must:

- Report pregnancies to the Ambrisentan REMS.
- Report a change or misclassification in reproductive status to the Ambrisentan REMS.
- Not distribute, transfer, loan, or sell ambrisentan, except to certified dispensers.
- Maintain and submit records of daily product dispensing data for female patients to the Ambrisentan REMS.
- 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.

For a list of Certified Pharmacies, call the Ambrisentan REMS at **1-888-417-3172**

Inpatient Pharmacy Dispensing:

Only inpatient pharmacies within institutions such as hospitals, long-term care facilities, and prisons that are certified in the Ambrisentan REMS may stock ambrisentan for patients being treated in the inpatient setting. In order for inpatients to receive ambrisentan, all inpatient pharmacies that wish to stock this product, must enroll in the Ambrisentan REMS and agree to comply with the requirements of the program.

Prior to dispensing, the inpatient pharmacy must:

- Verify that the female patient is:
 - Under the supervision and care of a certified prescriber
 - Enrolled or will be enrolled in the REMS prior to discharge
- Verify female patient's reproductive status
- For female of reproductive potential:
 - Verify that the pregnancy testing is complete
 - Counsel the patient on the risk of embryo-fetal toxicity and the need to use highly reliable contraception during treatment and for one month after stopping treatment
 - Counsel patient on the need to get monthly pregnancy tests and the need to inform the prescriber of a pregnancy immediately

Prior to discharge of a patient, the inpatient pharmacy must:

- Dispense no more than a 15 days' supply upon discharge.

At all times, the inpatient pharmacy must:

- Report pregnancies to the Ambrisentan REMS.
- Report a change or misclassification in reproductive status to the Ambrisentan REMS.
- Not distribute, transfer, loan, or sell ambrisentan, except to certified dispensers.
- Maintain records that all processes and procedures are in place and are being followed.
- 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.

The Ambrisentan REMS

- Enters every ambrisentan prescriber, female patient, and enrolled pharmacy into the Ambrisentan REMS database
- Collects all **Patient Enrollment Forms, Prescriber Enrollment Forms, Pharmacy Enrollment Forms (Outpatient and Inpatient), and Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Forms**
- Allow access to the certified pharmacies for verification of patient and prescriber information
- Collects information about changes in reproductive status, annual verification of reproductive status for Pre-Pubertal Females, and any occurrences of pregnancies during ambrisentan treatment or within one month following treatment discontinuation

