

PS-AMBRISENTAN RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Please visit www.PSAmbrisentanREMS.com or call **1-888-301-0333** 9am to 5pm ET, Monday - Friday

Prescriber Guide for the PS-Ambrisentan REMS

PS-Ambrisentan
— REMS —

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PS-Ambrisentan REMS

Indication

Ambrisentan is an endothelin receptor antagonist 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 are 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 after stopping treatment.

PS-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 PS-Ambrisentan REMS helps ensure the benefits of ambrisentan outweigh the risk of embryo-fetal toxicity. The goal of the PS-Ambrisentan REMS is to mitigate the risk of embryo-fetal toxicity associated with ambrisentan by:

1. Ensuring prescribers are educated on the following:
 - the risk of embryo-fetal toxicity
2. Ensuring prescribers are educated on and adhere to the following:
 - counseling patients about the risk and the need for monthly monitoring
 - enrolling patients in the PS-Ambrisentan REMS
 - monitoring patients at baseline and monthly
3. Ensuring that pharmacies are educated on the following:
 - the risk 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 ambrisentan
5. Ensuring that patients are informed about:

- the risk of embryo-fetal toxicity
- appropriate baseline and monthly patient monitoring
- appropriate contraception

Overview of the PS-Ambrisentan REMS

- Ambrisentan is only available to females through a restricted distribution program
- Prescribers must enroll in the PS-Ambrisentan REMS and comply with the PS-Ambrisentan REMS requirements to prescribe ambrisentan, even if you have previously enrolled in the Letairis REMS.
- All female patients must enroll in the PS-Ambrisentan REMS to receive ambrisentan, even if the patient has been previously enrolled in the Letairis REMS
- Prescribers must counsel Females of Reproductive Potential and Pre-pubertal Females on the risks of ambrisentan, including the risk of serious birth defects. The parent/guardian of the Pre-pubertal Female must also be 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 after stopping treatment

Summary of the PS-Ambrisentan REMS Requirements by Patient Category

Requirements	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 PS-Ambrisentan REMS	×	×	×	×
Counseling with the <i>Guide for Female Patients</i> , including the risk of embryo-fetal toxicity	×	×		
Prescriber must order and review pregnancy tests prior to initiation of treatment, monthly during treatment, and for one month after stopping treatment	×			
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 eight years of age and older		×		
Prescriber must submit a <i>Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form</i> within 10 business days of becoming aware of a change in reproductive status	×	×	×	×

*Counsel Pre-pubertal Female patient and parent/guardian

Your Role in the PS-Ambrisentan REMS

Prescribers must complete the following steps in the PS - Ambrisentan REMS:

To become certified to prescribe, the prescriber must:

- Review the drug's *Prescribing Information* and this guide and agree to comply with the PS-Ambrisentan REMS requirements.
- Enroll in the REMS by completing the ***Prescriber Enrollment Form*** and submitting it to the REMS, even if previously enrolled in the Letairis REMS. Complete the form online at www.PSAmbrisentanREMS.com, on the prescriber mobile app, or fax the completed form to the REMS Coordinating Center at 1-888-870-1819.

Before treatment initiation, the prescriber must:

- For all females: Assess the patient's reproductive status using the definitions on page 6 of this guide. Document and submit the results to the REMS using the ***Patient Enrollment Form***.
- For all females: Counsel the patient that the drug is only available through a restricted distribution program called the PS-Ambrisentan REMS.

- 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***.
- For Females of Reproductive Potential: Assess the patient's pregnancy status by ordering and reviewing her pregnancy test result.
- For Pre-pubertal Females: Counsel the patient and her parent/guardian about the risk of embryo-fetal toxicity using the ***Guide for Female Patients***.
- Enroll all female patients by completing the ***Patient Enrollment Form*** and submitting it to the REMS.

During treatment; before each prescription, the prescriber must:

- 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.
- For Females of Reproductive Potential: Assess the patient's pregnancy status by ordering and reviewing her pregnancy test result (OPTIONAL-may document

pregnancy test has been completed on the REMS website, mobile application, or by calling the REMS Coordinating Center).

During treatment; at least annually, the prescriber must:

- For Pre-pubertal Females at least age 8 or older: Document reproductive status and submit to the REMS at least annually using ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form***.

After treatment discontinuation; for one month, the prescriber must:

- For Females of Reproductive Potential: Assess the patient's pregnancy status by ordering and reviewing her pregnancy test result.

At all times, the prescriber must:

- For Pre-pubertal Females: Assess the patient's reproductive status.
- Report pregnancies to the REMS.

At all times, within 10 business days, the prescriber must:

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

Female Reproductive Status Definitions

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 in the following column)

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

For Females of Reproductive Potential:

Before treatment initiation:

- Assess the patient's reproductive status using the definitions on page 6 of this guide. Document and submit the results to the REMS using the ***Patient Enrollment Form***.
- Counsel the patient that the drug is only available through a restricted distribution program.
- Counsel the patient on the risk of embryo-fetal toxicity, the need to use highly reliable contraception (see page 10) during treatment and for one month following treatment discontinuation, and emergency contraception using the ***Guide for Female Patients***
- Assess the patient's pregnancy status by ordering and reviewing her pregnancy test results.
- Enroll the patient by completing the ***Patient Enrollment Form*** and submitting it to the REMS.

During treatment; before each prescription:

- Counsel the patient if she is not complying with the required testing or if she is not using appropriate contraception
- Assess the patient's pregnancy status by ordering and reviewing her pregnancy test result.

After treatment discontinuation; for one month:

- Assess the patient's pregnancy status by ordering and reviewing her pregnancy test result.

At all times:

- Report pregnancies to the REMS.

For Females of Non-Reproductive Potential:

For Pre-pubertal Females:

Before treatment initiation:

- Assess the patient's reproductive status using the definitions on page 6 of this guide. Document and submit the results to the REMS using the ***Patient Enrollment Form***.
- Counsel the patient and parent/guardian that the drug is only available through a restricted distribution program.
- Counsel the patient and parent/guardian on the risk of embryo-fetal toxicity using the ***Guide for Female Patients***.
- Enroll the patient by completing the ***Patient Enrollment Form*** and submitting it to the REMS.

During treatment; at least annually:

- For patients at least age 8 or older, document the patient's reproductive status and submit to the REMS using the **Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form**

At all times:

- Assess the patient's reproductive status.
- Report pregnancies to the REMS.

For Post-Menopausal Females:

Before treatment initiation:

- Assess the patient's reproductive status using the definitions on page 6 of this guide. Document and submit the results to the REMS using the ***Patient Enrollment Form***.
- Counsel the patient and parent/guardian that the drug is only available through a restricted distribution program.
- Enroll the patient by completing the ***Patient Enrollment Form*** and submitting it to the REMS.

At all times:

- Report pregnancies to the REMS.

For Females with Other Medical Reasons for Permanent, Irreversible Infertility:

Before treatment initiation:

- Assess the patient's reproductive status using the definitions on page 6 of this guide. Document and submit the results to the REMS using the Patient Enrollment Form.
- Counsel the patient and parent/guardian that the drug is only available through a restricted distribution program.
- Enroll the patient by completing the Patient Enrollment Form and submitting it to the REMS.

At all times:

- Report pregnancies to the REMS.

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 on the next page 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 PS-Ambrisentan REMS Coordinating Center (by phone at 1-888-301-0333) of any pregnancies that occur during treatment or within one month of discontinuation.

Contraceptive Options for Females of Reproductive Potential

OPTION 1

One method from this list:
Standard intrauterine device (CopperT380AIUD)
Intrauterine system (LNg20 IUS - progesterone IUD)
Tubal sterilization
Progesterone implant

OR

OPTION 2

One method from this list:
Estrogen and progesterone oral contraceptives (“the pill”)
Estrogen and progesterone transdermal patch
Vaginalring
Progesterone injection

+

One method from this list:
Male condom
Diaphragm with spermicide
Cervical cap with spermicide

OR

OPTION 3

One method from this list:
Diaphragm with spermicide
Cervical cap with spermicide

+

This method:
Male condom

OR

OPTION 4

This method:
Partner’s vasectomy

+

One method from this list:
Male condom
Diaphragm with spermicide
Cervical cap with spermicide
Estrogen and progesterone oral contraceptives (“the pill”)
Estrogen and progesterone transdermal patch
Vaginalring
Progesterone injection

The PS-Ambrisentan REMS Coordinating Center

- Contacts Females of Reproductive Potential receiving ambrisentan each month and one month after discontinuing treatment to confirm completion of pregnancy testing, inform them on the risk of embryo-fetal toxicity, the need to use highly reliable contraception during ambrisentan treatment and for one month following treatment discontinuation, and emergency contraception.
 - Contact will occur through the patient's preferred method of contact
- Collects information about changes in reproductive status, annual verification of reproductive potential status for Pre-pubertal Females, and any occurrences of pregnancies during ambrisentan treatment or within one month of treatment discontinuation

Choosing an Enrolled Pharmacy

Pharmacies that dispense ambrisentan must be enrolled in the PS-Ambrisentan REMS. Both community and specialty pharmacies participate in the PS-Ambrisentan REMS. Your patient should decide what type of pharmacy is best for her. You may need to help your patients find a pharmacy enrolled in the PS-Ambrisentan REMS.

For a list of enrolled pharmacies, visit **www.PSAmbrisentanREMS.com** or call the PS-Ambrisentan REMS Coordinating Center at 1-888-301-0333. Your patient may also contact her insurance carrier for assistance in determining what pharmacies and ambrisentan products are supported by her current insurance plan.

Options for Performing Prescriber Actions in the PS-Ambrisentan REMS

Depending on the activity, prescriber actions described in this guide can be completed via the following methods: online at www.PSAmbrisentanREMS.com, on the prescriber mobile app, or by faxing a completed form to the PS-Ambrisentan REMS Coordinating Center at 1-888-870-1819. The following table provides a guide as to which prescribers' actions can be completed by what method.

Activity	Online	Prescriber App	Fax
Prescriber Enrollment	X	X	X
Patient Enrollment	X	X	X
Report a Change in Reproductive Status	X	X	X
Find a Pharmacy	X	X	

Additional questions

Please visit www.PSAmbrisentanREMS.com or call the PS-Ambrisentan REMS Coordinating Center at **1-888-301-0333** for more information about the PS-Ambrisentan REMS.

Please see the Prescribing Information including the **BOXED WARNING** for more complete safety information.

