

Prescriber Guide for the Letairis REMS Program

Changes to the Letairis Risk Evaluation and Mitigation Strategy (REMS) Program (November 2018)

- Revised: *Prescriber Guide for the Letairis REMS Program*: Risk of teratogenicity and removal of Medication Guide
- Revised title and content: *Letairis REMS Program Guide for Females Who Can Get Pregnant* to *Letairis REMS Program Guide for Female Patients*
- Removal of the Medication Guide from REMS materials
 - Revised form: *Letairis REMS Patient Enrollment and Consent Form*
 - Revised form: *Prescriber Enrollment and Agreement Form*
- Updated: REMS Website (www.letairisrems.com)

This guide is part of an FDA-approved REMS.



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Letairis REMS Program

Indication

Letairis 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
- In combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability

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 teratogenicity

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

Pregnancy must be excluded prior to the initiation of Letairis treatment, monthly thereafter, and for 1 month after stopping treatment.

Letairis REMS Program

Because of the risk of serious birth defects, Letairis is only available to females through a restricted distribution program under an FDA-required REMS. The Letairis REMS helps ensure the benefits of Letairis outweigh the risk of teratogenicity. The purposes of the Letairis REMS Program are to:

- Inform and educate healthcare providers and female patients about the risk of teratogenicity associated with the use of Letairis
- Minimize the risk of fetal exposure and adverse fetal outcomes in Females of Reproductive Potential
 - Females who are pregnant must not be prescribed Letairis
 - Females taking Letairis must not become pregnant

Changes to the Letairis REMS Program

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Overview of the Letairis REMS Program

- Letairis is only available to females through a restricted distribution program
- Prescribers must enroll in the Letairis REMS Program and comply with the Letairis REMS Program requirements to prescribe Letairis
- All female patients must enroll in the Letairis REMS Program to receive Letairis
- Prescribers must educate and counsel Females of Reproductive Potential and Pre-Pubertal Females on the risks of Letairis, including the risk of serious birth defects. The parent/guardian of the Pre-Pubertal Female must also be educated and counseled on the risks of Letairis
- Prescribers must order and review pregnancy tests for Females of Reproductive Potential prior to initiation of treatment, monthly during treatment, and for 1 month after stopping treatment

Summary of the Letairis REMS Program Requirements by Patient Category

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 Letairis REMS Program	×	×	×	×
Counseling with <i>Letairis REMS Program Guide for Female Patients</i>	×	×		
Prescriber must order and review pregnancy tests prior to initiation of treatment, monthly during treatment, and for 1 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 8 years of age and older		×		
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 potential status within 10 business days of awareness	×	×	×	×

^{*}Counsel Pre-Pubertal Female patient and parent/guardian

Your Role in the Letairis REMS Program

Prescribers must complete the following steps in the Letairis REMS Program:

1. Read the Letairis Prescribing Information and this guide to understand the Letairis REMS Program and the risks of Letairis

2. Complete the Prescriber Enrollment and Agreement Form

- You will attest to understanding the risks of Letairis and agree to comply with the requirements of the Letairis REMS Program
- Complete the form online at www.letairisrems.com or fax the completed form to the Letairis REMS Coordinating Center at **1-888-882-4035**

3. Determine the reproductive potential 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 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

4. Educate/counsel all female patients about risks of Letairis and about the Letairis REMS Program

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

For Females of Reproductive Potential:

- Review with the Female of Reproductive Potential the *Letairis REMS Program Guide for Female Patients* prior to initiating treatment
- Educate Females of Reproductive Potential about the risk of teratogenicity, the need to use highly reliable contraception (see page 7) during Letairis treatment and for 1 month following treatment discontinuation, and the need to use emergency contraception, if required
- Order and review pregnancy tests prior to initiation of Letairis treatment, monthly during treatment, and for 1 month after stopping Letairis treatment
- Advise the patient of the requirement for monthly pregnancy tests to confirm they are not pregnant so they can receive Letairis
- Counsel the Female of Reproductive Potential if she is not complying with the Letairis REMS Program requirements
- 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 potential status

For Females of Non-Reproductive Potential:

For Pre-Pubertal Females:

- Educate the Pre-Pubertal Female patient and parent/guardian about the risk of teratogenicity and review the *Letairis REMS Program Guide for Female Patients* with the patient and parent/guardian
- Evaluate regularly Pre-Pubertal Females for any changes in reproductive status while receiving Letairis
- Verify the reproductive potential status annually for Pre-Pubertal Females who are at least 8 years of age and older by completing the *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*
- Report any misclassification or change in reproductive potential status by completing the *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form* within 10 business days of becoming aware of the change

For Post-Menopausal Females:

- Report any misclassification in reproductive potential status by completing 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:

- Report any misclassification in reproductive potential status by completing 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 tests for the patient:
 - Prior to initiating treatment
 - Monthly during treatment
 - 1 month after stopping treatment

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 Letairis REMS Coordinating Center if she becomes pregnant while on Letairis or within 1 month of stopping treatment.

6. Enroll all female patients into the Letairis REMS Program

- Access, complete and submit the Letairis REMS patient enrollment online at www.letairisrems.com. Alternatively, complete a paper version of the *Letairis REMS Patient Enrollment and Consent Form* and fax the completed form, along with all patient insurance information, including prescription drug benefits and medical benefits, to the Letairis REMS Coordinating Center at **1-888-882-4035**
- Keep the original form with the patient's records

7. Evaluate reproductive potential status of female patients throughout treatment

- Report any change in patient's reproductive potential status within 10 business days of becoming aware of the change to the Letairis REMS Coordinating Center by faxing the completed *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form* to **1-888-882-4035**

- Verify the reproductive potential status of Pre-Pubertal Females who are at least 8 years of age or older annually by completing the *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*
- Counsel females who fail to comply with the Letairis REMS Program requirements
- Notify the Letairis REMS Coordinating Center of any adverse events, or if any patient becomes pregnant during Letairis treatment or within 1 month of stopping treatment

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 *Letairis REMS 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 Letairis REMS Coordinating Center (by phone at 1-866-664-5327) of any pregnancies that occur during treatment or within 1 month of discontinuation**

Contraceptive Options for Females of Reproductive Potential

OPTION 1

One method from this list:

Standard intrauterine device
 (Copper T 380A IUD)

Intrauterine system
 (LNg 20 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

Vaginal ring

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

Vaginal ring

Progesterone injection

Role of Certified Pharmacies

- Contact all Females of Reproductive Potential receiving Letairis each month to confirm completion of pregnancy testing, and counsel them on the risk of teratogenicity
- Ship Letairis to the patient/caregiver

For a list of Certified Pharmacies, call the Letairis REMS Coordinating Center at **1-866-664-5327**

The Letairis REMS Coordinating Center

- Enters every Letairis prescriber and female patient into the Letairis REMS Program database
- Collects all *Letairis REMS Patient Enrollment and Consent Forms and Prescriber Enrollment and Agreement Forms*
- Sends patient information to the chosen Certified Pharmacy
- Collects information about adverse events, changes in reproductive status, annual verification of reproductive potential status for Pre-Pubertal Females, and any occurrences of pregnancies during Letairis treatment or within 1 month of treatment discontinuation

Additional questions

Please visit www.letairisrems.com or call the Letairis REMS Coordinating Center at **1-866-664-5327** for more information about the Letairis REMS Program.

Please see the accompanying patient Medication Guide and Prescribing Information, including **BOXED WARNING**, for more complete information.



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Letairis[®]
ambriesentan
5 mg and 10 mg Tablets