

NDA 22-081 Letairis® (ambrisentan)

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

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I. GOAL(S):

The goals of the Letairis Risk Evaluation and Mitigation Strategy (REMS) Program are:

1. To inform prescribers, patients, and pharmacists about the serious risk of teratogenicity and safe-use conditions for Letairis
2. To minimize the risk of fetal exposure and adverse fetal outcomes in Females of Reproductive Potential (FRP) prescribed Letairis
 - a. Females who are pregnant must not be prescribed Letairis
 - b. Females taking Letairis must not become pregnant

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each Letairis prescription in accordance with 21CFR 208.24.

The [Medication Guide](#) is part of the REMS and is appended.

B. Elements To Assure Safe Use

1. Healthcare providers who prescribe Letairis will be specially certified.
 - a. Gilead will ensure that physicians and other appropriately licensed healthcare professionals who prescribe Letairis are specially certified. Gilead will ensure that, to become certified, each prescriber agrees, on the *Prescriber Enrollment and Agreement Form*, that he or she has read the full prescribing information (PI), the *Letairis Medication Guide*, and the *Prescriber Guide to the Letairis REMS Program*. The physician further agrees that he or she will:
 - i) Enroll all females in the Letairis REMS program
 - ii) Determine whether each female is of reproductive potential as defined in the *Prescriber Guide to the Letairis REMS Program*

- iii) Advise all females that Letairis is only available through a restricted distribution program called the Letairis REMS program
- iv) For FRP:
 - (1) Educate FRPs about the risk of teratogenicity, the need to use highly reliable contraception as defined in the *Prescriber Guide to the Letairis REMS Program* during Letairis treatment and for one month following treatment discontinuation, and the need to use emergency contraception if required
 - (2) Order and review pregnancy tests prior to initiation of Letairis treatment, monthly during treatment, and for one month after stopping Letairis treatment
 - (3) Counsel a female patient if she is not complying with the required testing or if she is not using appropriate contraception as specified for FRP
 - (4) Review with FRP, the *Letairis Medication Guide* and the *Letairis REMS Program Guide for Females Who Can Get Pregnant* prior to initiating treatment
 - (5) Report any changes in reproductive 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
- v) For Pre-Pubertal Females:
 - (1) Educate Pre-Pubertal Female patient and parent/guardian about the risk of teratogenicity
 - (2) Review the *Letairis Medication Guide* with the patient and parent/guardian
 - (3) Regularly evaluate Pre-Pubertal Females for any change in reproductive status while receiving Letairis
 - (4) Verify and document status as Pre-Pubertal Female at least 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*
 - (5) Report any change in reproductive 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
- vi) For Post-Menopausal Females:
 - (1) 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.

- (2) Report adverse events and any pregnancies during Letairis treatment to Gilead with all available information required for the Form FDA 3500A
- vii) For Females with Other Medical Reasons for Permanent, Irreversible Infertility:
- (1) 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.
 - (2) Report adverse events and any pregnancies during Letairis treatment to Gilead with all available information required for the Form FDA 3500A
- b. Gilead will:
- i) Ensure that prescribers' enrollment information and date of agreement are linked to their enrolled female patients' information in a validated database
 - ii) For all females, ensure that the patient information from a new prescriber is linked in the Letairis REMS program database with information from the prior prescriber
 - iii) Ensure that the Letairis REMS Coordinating Center annually contacts the prescriber of a Pre-Pubertal Female to ensure that the prescriber verifies the Pre-Pubertal Female's reproductive status by completing the *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*
 - iv) Maintain a validated database of certified prescribers in the Letairis REMS program. Gilead will ensure that prescribers' certification requirements are met and may de-enroll noncompliant prescribers until the requirements are met
 - v) Ensure that within 60 days of REMS modification approval, all materials listed in or appended to the Letairis REMS will be available through the Letairis REMS program website (www.letairisrems.com) or by calling the Letairis REMS Coordinating Center at 1-866-664-5327
- c. The following materials are part of the Letairis REMS program and are appended:
- i) *Prescriber Enrollment and Agreement Form*
 - ii) *Prescriber Guide to the Letairis REMS Program*
 - iii) *Letairis REMS Program Guide for Females Who Can Get Pregnant*
 - iv) *Patient Enrollment and Consent Form*
 - v) *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*
 - vi) *Letairis REMS website (www.letairisrems.com)*

2. Pharmacies, practitioners, and health care settings that dispense Letairis (dispensers) will be specially certified.
 - a. Gilead will ensure that pharmacies, practitioners, and health care settings that dispense Letairis are specially certified. Gilead will ensure that, to be certified, pharmacies, practitioners, and health care settings that dispense Letairis attest that:
 - i) For all female patients, they will dispense Letairis only to patients enrolled in the Letairis REMS program
 - ii) Certified pharmacies will dispense Letairis to female patients only after receipt of patient enrollment form from the Letairis REMS Coordinating Center
 - iii) Certified pharmacies will confirm any change in a female patient's reproductive potential status through the Letairis REMS Coordinating Center
 - iv) Provide a *Letairis Medication Guide* to patients each time Letairis is dispensed
 - v) For FRP (as defined in the *Prescriber Guide to the Letairis REMS Program*):
 - (1) Counsel FRP on the risk of serious birth defects and the need to use highly reliable contraception (as defined in the *Prescriber Guide to the Letairis REMS Program*) during Letairis treatment and for one month after stopping Letairis treatment
 - (2) Inform FRP of the need to complete a monthly pregnancy test and to inform their prescriber immediately if they suspect they may be pregnant
 - (3) Speak with each FRP, or their prescriber, every month before dispensing Letairis to obtain confirmation that pregnancy testing was completed
 - (4) Dispense Letairis to FRP no more than a 30-day supply and only upon completing the following process:
 - (a.) Obtain confirmation from FRP that the pregnancy testing was completed
 - (b.) If unable to obtain confirmation from FRP that the pregnancy testing was completed, or if the FRP cannot be reached, the certified pharmacy will obtain confirmation from the patient's prescriber
 - (c.) If the prescriber for the FRP cannot confirm that the pregnancy testing was completed, the certified pharmacy will:
 - i. Remind the prescriber of his/her obligation to order and review monthly pregnancy tests

- ii. Ask the prescriber whether or not he/she authorizes the refill of Letairis. The FRP is eligible to receive a 30-day supply of Letairis only if the prescriber authorizes the refill of Letairis
 - vi) Notify Gilead of reports of adverse events and any reports of pregnancy and provide all available information needed for FDA Form 3500A
 - vii) Certified pharmacies will provide daily product dispensing data for FRP to the Letairis REMS Coordinating Center
- b. Gilead will ensure the Letairis REMS Coordinating Center notifies certified pharmacies of patients' change in reproductive status within one business day of receipt of completed *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*
- c. Gilead will ensure that a designated representative of each certified pharmacy:
- i) Is trained on the requirements of the Letairis REMS program
 - ii) Trains dispensing staff on the Letairis REMS program procedures and Letairis REMS materials as described above prior to dispensing Letairis to FRP
 - iii) Agrees that the certified pharmacy may be audited by the FDA, Gilead, or a third party designated by Gilead
3. Letairis will be dispensed to FRP with evidence or other documentation of safe-use conditions:
- a. Gilead will ensure that FRP treated with Letairis are enrolled in the Letairis REMS program and assigned a unique patient identification number, before Letairis is dispensed by a certified pharmacy. Gilead will ensure that, to become enrolled, or when changing prescribers, each FRP must sign a *Patient Enrollment and Consent Form* acknowledging that she has read the *Letairis Medication Guide* and the *Letairis REMS Program Guide for Females Who Can Get Pregnant*. By enrolling, the FRP agrees:
 - i) To be contacted, prior to each shipment of Letairis, to obtain confirmation that pregnancy testing was completed
 - ii) To be counseled on the requirements of the Letairis REMS program and the risks of Letairis
 - iii) To be contacted by Gilead or the Letairis REMS Coordinating Center if she becomes pregnant while on Letairis or within 30 days after treatment discontinuation

C. Implementation System

The Implementation System will include the following:

1. Gilead will maintain a validated database of certified dispensers and females enrolled in the Letairis REMS program to monitor and evaluate implementation of the elements provided for under Sections B.2 and B.3 above
2. Gilead will monitor the distribution of Letairis to ensure that the drug is only shipped to certified dispensers.
3. Gilead will track Letairis dispensing and review the location and amount of medication dispensed by certified pharmacies to FRPs.
4. Gilead will audit all certified pharmacies and the Letairis REMS Coordinating Center at the initiation of the Letairis REMS program to ensure they implement the program as directed. Thereafter, Gilead will include the certified pharmacies and the Letairis REMS Coordinating Center in the company's annual audit plan
5. Gilead will monitor and evaluate the implementation of the elements provided for under Sections B.1, B.2, and B.3, above, in the manner described in the Letairis REMS Supporting Document, and take reasonable steps to work to improve implementation of these elements
6. Gilead will monitor the certified pharmacies to ensure their compliance with the Letairis REMS program and will institute corrective actions if they are found non-compliant

D. Timetable for Submission of Assessments

Gilead will submit Letairis REMS assessments to the FDA annually no later than August 13th. 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 days before the submission date for that REMS assessment. Gilead will submit each REMS assessment so that it will be received by the FDA on or before the due date.