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GILEAD SCIENCES, INC

NDA 22-081 LETAIRIS (ambrisentan)
Gilead Sciences, Inc.
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Boulder, CO 80301

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

The risk minimization goals of the LETAIRIS Risk Evaluation and Mitigation Strategy (REMS) are:

1. To encourage informed benefit-risk decisions regarding the use of LETAIRIS
2. To minimize the risk of hepatotoxicity in patients prescribed LETAIRIS
3. To minimize the risk of fetal exposure and adverse fetal outcomes in female patients of childbearing potential prescribed LETAIRIS
    a. Women who are pregnant must not be prescribed LETAIRIS
    b. Women taking LETAIRIS must not become pregnant

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each 30-day supply of LETAIRIS and in accordance with 21CFR 208.24.

B. Elements To Assure Safe Use

1. Healthcare providers who prescribe LETAIRIS will be specially certified under 505-1(f)(3)(A).
    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) and Medication Guide for LETAIRIS. The physician further agrees that he or she will:
        i) Enroll all patients who take LETAIRIS in the REMS program
        ii) Re-enroll patients into the REMS program after the first 12 months of treatment then annually thereafter
        iii) Review the LETAIRIS Medication Guide and Patient Educational Brochure with every patient

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iv) Determine whether each female is of childbearing potential as defined in the Prescriber Enrollment and Agreement Form before enrolling her in the REMS

v) Monitor the status of each female to determine when she becomes a female of childbearing potential

vi) Educate all female patients of childbearing potential who take LETAIRIS about the need to use highly reliable contraception as defined in the Prescriber Enrollment and Agreement Form during LETAIRIS treatment and for one month following treatment discontinuation

vii) Discuss the risks of LETAIRIS, including the risks of hepatotoxicity and teratogenicity with each patient prior to prescribing LETAIRIS.

viii) Order and review liver function tests (including aminotransferases and bilirubin) and pregnancy tests (for female patients of childbearing potential) prior to initiation of LETAIRIS treatment and monthly during treatment

ix) Counsel the patient if the patient is not complying with the required testing or, for female patients of childbearing potential, if she is not using appropriate contraception

x) Report any adverse events, including liver injury, and any patient who becomes pregnant during LETAIRIS treatment to Gilead with all available information required for the FDA form 3500A.

b. Gilead will:

i) Ensure that prescribers' enrollment information and date of agreement is linked to their enrolled patients' information in a validated database

ii) Ensure that the patient information from a new prescriber is linked in the REMS program database with information from the prior prescriber.

iii) Ensure that any prescriber who prescribes LETAIRIS within six months of his/her enrollment to fewer than six patients completes Prescriber Supplemental Education on the REMS program requirements by agreeing on the Ongoing Education Program Form that they have received the supplemental educational materials and understand the REMS program requirements and the risks of Letairis.

c. Gilead will maintain a database of certified prescribers in the REMS program. Gilead will ensure that prescribers' certification requirements are met and may de-enroll noncompliant prescribers until the requirements are met.

d. The following materials are part of the REMS and are appended:

i) Prescriber Enrollment and Agreement Form

ii) Prescriber Educational Brochure

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iii) Patient Educational Brochures

iv) Prescriber Supplemental Education Materials

(1) Ongoing Education Program Form

2. Pharmacies, practitioners, and health care settings that dispense LETAIRIS (dispensers) will be specially certified under 505-1(f)(3)(B).

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 they will:

i) Receive and accept prescriber and patient enrollment forms only from the REMS Coordinating Center

ii) Counsel patients

(1) on the risks of LETAIRIS, including the risks of liver injury and serious birth defects

(2) on the need to complete a monthly liver function test and pregnancy test (for female patients of childbearing potential as defined in the Prescriber Enrollment and Agreement Form)

iii) Counsel all female patients of childbearing potential on the need to use highly reliable contraception (as defined in the Prescriber Enrollment and Agreement Form) during LETAIRIS treatment and for one month after treatment discontinuation, and the need to inform their prescriber immediately if they suspect they may be pregnant

iv) For product that will be dispensed and shipped to the patient, confirm the drug shipment address with the patient

v) Dispense LETAIRIS only as 30-day supplies and require monthly refills

vi) Dispense LETAIRIS only to patients enrolled in the REMS program

vii) Provide a Medication Guide to patients each time LETAIRIS is dispensed

viii) Speak with each patient, or their prescriber, every month before dispensing LETAIRIS to obtain confirmation that liver function testing and, for female patients of childbearing potential, pregnancy testing was completed.

ix) Dispense a 30-day supply of LETAIRIS only upon completing the following process:

(1) Obtain confirmation from the patient that the testing was completed.

(2) If unable to obtain confirmation from the patient that the testing was completed, or if the patient cannot be reached, the

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certified dispenser will obtain confirmation from the patient's prescriber.

(3) If the patient's prescriber cannot confirm that the required testing was completed, the certified dispenser will:

(a) Remind the prescriber of his/her obligation to order and review monthly liver function tests and pregnancy tests (for female patients of childbearing potential)

(b) Ask the prescriber whether or not he/she authorizes the refill of LETAIRIS. The patient is eligible to receive a 30-day supply of LETAIRIS only if the prescriber authorizes the refill of LETAIRIS.

x) Call patients, who discontinue LETAIRIS treatment, or their prescriber, to determine the reason for treatment discontinuation and record this information in the validated database

xi) Notify Gilead of any reports of adverse events, including liver injury, and any reports of pregnancy and provide all available information needed for FDA form 3500A.

xii) Complete an inventory tracking log for every time LETAIRIS is dispensed

xiii) Provide daily product dispensing data to the REMS Coordinating Center

b. Gilead will ensure that a designated representative of each certified dispenser:

i) is trained on the REMS program.

ii) trains dispensing staff on the REMS program procedures and REMS materials as described above prior to dispensing Letairis

iii) agrees that the certified dispenser may be audited by the FDA, Gilead, or a third party designated by Gilead

3. Letairis will be dispensed to patients with evidence or other documentation of safe-use conditions under 505-1(f)(3)(D):

a. Gilead will ensure that patients treated with LETAIRIS are enrolled in the REMS program and assigned a unique identifying number, before LETAIRIS is dispensed to him or her. Gilead will ensure that, to become enrolled, or when changing prescribers, each patient must sign a patient enrollment form acknowledging that he or she:

i) has read the LETAIRIS Medication Guide and patient educational materials and

ii) agrees to be contacted, prior to each shipment of LETAIRIS, to obtain confirmation that liver function testing and pregnancy testing was completed and

iii) agrees to be counseled on the requirements of the REMS program and

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the risks of LETAIRIS.

iv) acknowledges, in the case of a female of childbearing potential that she will be contacted by the Gilead DSPH Department if she becomes pregnant while on LETAIRIS or within 30 days after treatment discontinuation

b. Gilead will ensure that, to continue receiving Letairis, each patient is re-enrolled every 12 months following their initial enrollment.

c. The following materials are part of the REMS and are appended:

i) Patient Enrollment and Consent Form

C. Implementation System

The Implementation System will include the following:

1. Gilead will maintain a database of certified dispensing entities and enrolled patients 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 to enrolled patients.
4. Gilead will audit all certified dispensers and the REMS coordinating center at the initiation of the REMS program to ensure they implement the program as directed. Thereafter, Gilead will include the certified dispensers and the REMS coordinating center in the company's annual audit planning.
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 REMS supporting document, and take reasonable steps to work to improve implementation of these elements.
6. Gilead will monitor the certified dispensers to ensure their compliance with the REMS program and will institute corrective actions if they are found non-compliant.

D. Timetable for Submission of Assessments

Following approval of the REMS, the REMS assessments will be submitted to the FDA annually. The assessment interval period will close no earlier than 60 days prior to the date the respective assessment is due. The assessment is to be received by the FDA on the due date.