Initial REMS Approval: 05/2009
Most Recent Modification: 02/2012

NDA 22-081 LETAIRIS® (ambrisentan)
RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

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 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 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 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 annually.

        iii) Review the LETAIRIS Medication Guide and Patient Enrollment Guide with every patient.

iv) For female patients, determine whether each female is of childbearing potential as defined in the Prescriber Enrollment and Agreement Form before enrolling her in the REMS and monitor each female patient for changes in childbearing potential status.

v) For female patients of childbearing potential:

(1) Educate patients about the risk of teratogenicity and 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.

(2) Order and review pregnancy tests prior to initiation of LETAIRIS treatment and monthly during treatment.

(3) Counsel the patient if the patient is not complying with the required testing or if she is not using appropriate contraception.

vi) Report any adverse events and any pregnancy 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 Guide: Letairis and the LEAP Program

iii) Patient Enrollment Guide

iv) Letairis Medication Guide

v) Patient Enrollment and Consent Forms

vi) Patient Re-enrollment Form

vii) Prescriber Supplemental Education Materials includes:

(1) Prescriber Guide: Letairis and the LEAP Program

(2) LEAP Patient Enrollment Guide

(3) Letairis Prescribing Information

(4) Letairis Medication Guide

(4) 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) Dispense LETAIRIS only to patients enrolled in the REMS program.

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

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

        v) For female patients of childbearing potential (as defined in the Prescriber Enrollment and Agreement Form):

            (1) Counsel patients on the risk of serious birth defects and 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.

            (2) Inform patients 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 patient, or their prescriber, every month before dispensing LETAIRIS to obtain confirmation that pregnancy testing was completed.

            (4) Dispense LETAIRIS only as a 30-day supply and only upon completing the following process:

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

                (b) If unable to obtain confirmation from the patient that the pregnancy testing was completed, or if the patient cannot be reached, the certified dispenser will obtain confirmation from the patient's prescriber.

(c) If the patient's prescriber cannot confirm that the pregnancy testing was completed, the certified dispenser 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 patient is eligible to receive a 30-day supply of LETAIRIS only if the prescriber authorizes the refill of LETAIRIS.

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

vii) Notify Gilead of any reports of adverse events and any reports of pregnancy and provide all available information needed for FDA Form 3500A.

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

ix) 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 has read the LETAIRIS Medication Guide and patient educational materials and, for female patients of childbearing potential, that they agree:

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 REMS program and the risks of LETAIRIS.

iii) To be contacted by the Gilead 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 by their prescriber following their initial enrollment.

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

Gilead will submit REMS assessments to the FDA annually on 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 assessment. Gilead will submit each assessment so that it will be received by the FDA on or before the due date.

Medication Guide
LETAIRIS® (le-TAIR-is)
(ambrisentan)
Tablets

Read this Medication Guide before you start taking LETAIRIS and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about LETAIRIS?

- **Serious birth defects.**

  LETAIRIS can cause serious birth defects if taken during pregnancy.

  - **Women must not be pregnant when they start taking LETAIRIS or become pregnant during treatment.**
  - Women who are able to get pregnant must have a negative pregnancy test before beginning treatment with LETAIRIS and each month during treatment. Your doctor will decide when to do the test, depending on your menstrual cycle.

  Women who are able to get pregnant must use two acceptable forms of birth control, during LETAIRIS treatment and for one month after stopping LETAIRIS.

  - If you have had a tubal sterilization or have an IUD, these methods can be used alone and no other form of birth control is needed.
  - Talk with your doctor or gynecologist (a doctor who specializes in female reproduction) to find out about how to prevent pregnancy.
  - **Do not have unprotected sex. Talk to your doctor or pharmacist right away if you have unprotected sex or if you think your birth control has failed. Your doctor may tell you to use emergency birth control.**
  - **Tell your doctor right away if you miss a menstrual period or think you may be pregnant.**

LETAIRIS is available only through a restricted program called the LETAIRIS Education and Access Program (LEAP). To receive LETAIRIS, you must talk to your doctor, understand the benefits and risks of LETAIRIS, and agree to all of the instructions in the LEAP program.

What is LETAIRIS?

LETAIRIS is a prescription medicine to treat pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of your lungs.

LETAIRIS can improve your ability to exercise and it can help slow down the worsening of your physical condition and symptoms.

Who should not take LETAIRIS?

Do not take LETAIRIS if:

- **you are pregnant, plan to become pregnant, or become pregnant during treatment with LETAIRIS. LETAIRIS can cause serious birth defects.** (See "What is the most important information I should know about LETAIRIS?") Serious birth defects from LETAIRIS happen early in pregnancy.

Tell your doctor about all your medical conditions and all the medicines you take including prescription and nonprescription medicines. LETAIRIS and other medicines may affect each other causing side effects. Do not start any new medicines until you check with your doctor.

Especially tell your doctor if you take the medicine cyclosporine (Gengraf, Neoral, Sandimmune). Your doctor may need to change your dose of LETAIRIS. You should not take more than 5 mg of LETAIRIS each day if you also take cyclosporine.

LETAIRIS has not been studied in children.

How should I take LETAIRIS?

LETAIRIS will be mailed to you by a specialty pharmacy. Your doctor will give you complete details.

- Take LETAIRIS exactly as your doctor tells you. Do not stop taking LETAIRIS unless your doctor tells you.
- You can take LETAIRIS with or without food.
- Do not split, crush or chew LETAIRIS tablets.
- It will be easier to remember to take LETAIRIS if you take it at the same time each day.
- If you take more than your regular dose of LETAIRIS, call your doctor right away.
- If you miss a dose, take it as soon as you remember that day. Take your next dose at the regular time. Do not take two doses at the same time to make up for a missed dose.

What should I avoid while taking LETAIRIS?

- **Do not get pregnant** while taking LETAIRIS. (See the serious birth defects section of "What is the most important information I should know about LETAIRIS?") If you miss a menstrual period, or think you might be pregnant, call your doctor right away.
- **Breastfeeding is not recommended** while taking LETAIRIS. It is not known if LETAIRIS can pass through your milk and harm your baby.

What are the possible side effects of LETAIRIS?

Serious side effects of LETAIRIS include:

- **Serious birth defects.** (See "What is the most important information I should know about LETAIRIS?")
- **Swelling all over the body** (fluid retention) can happen within weeks after starting LETAIRIS. Tell your doctor right away if you have any unusual weight gain, tiredness, or trouble breathing while taking LETAIRIS. These may be symptoms of a serious health problem. You may need to be treated with medicine or need to go to the hospital.

- **Sperm count reduction.** Reduced sperm counts have been observed in some men taking a drug similar to LETAIRIS, an effect which might impair their ability to father a child. Tell your doctor if remaining fertile is important to you.
- **Low red blood cell levels** (anemia) can happen during the first weeks after starting LETAIRIS. If this happens, you may need a blood transfusion. Your doctor will do blood tests to check your red blood cells before starting LETAIRIS. Your doctor may also do these tests during treatment with LETAIRIS.

The most common side effects of LETAIRIS are:

- Swelling of hands, legs, ankles and feet (peripheral edema)
- Stuffy nose (nasal congestion)
- Inflamed nasal passages (sinusitis)
- Hot flashes or getting red in the face (flushing)

Some medicines that are like LETAIRIS can cause liver problems. Tell your doctor if you get any of these symptoms of a liver problem while taking LETAIRIS:

- loss of appetite
- nausea or vomiting
- fever
- achiness
- generally do not feel well
- pain in the upper right stomach (abdominal) area
- yellowing of your skin or the whites of your eyes
- dark urine
- itching

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of LETAIRIS. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LETAIRIS?

Store LETAIRIS at 59 F to 86 F (15 C to 30 C), in the package it comes in.

Keep LETAIRIS and all medicines out of the reach of children.

General information about LETAIRIS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LETAIRIS for a condition for which it was not prescribed. Do not give LETAIRIS to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about LETAIRIS. If you would like more information, ask your doctor. You can ask your doctor or pharmacist for information about LETAIRIS that is written for healthcare professionals.

For more information, call 1-866-664-LEAP (5327) or visit www.letairis.com or www.gilead.com.

What are the ingredients in LETAIRIS?

Active ingredient: ambrisentan

Inactive Ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The tablets are film-coated with a coating material containing FD&C Red #40 aluminum lake, lecithin, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Revised February 2012

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Gilead Sciences, Inc., Foster City, CA 94404

GS22-081-009

LEAP

LETAIRIS Education and Access Program (LEAP)

LEAP Prescriber Enrollment and Agreement Form

To be enrolled into the LETAIRIS Education and Access Program, complete and fax the front of this form. **FAX:** 1-888-882-4035

Prescriber Information

First Name: _____ Middle Initial: _____ Last Name: _____ Suffix: _____

Specialty: _____ Name of Facility: _____ Office Contact: _____

Address: _____ City: _____ State: _____ ZIP: _____

E-mail: _____ Phone: (____) _____ Fax: (____) _____

State License No.: _____ NPI No.: _____ DEA No.: _____

Prescriber Agreement

By signing below, you signify your understanding of the risks of Letairis® (ambrisentan) treatment and your obligation as a LETAIRIS prescriber to educate your patients about these risks, counsel them on risk reduction, monitor them appropriately, and report adverse events to LEAP. Specifically, you attest to the following:

- I have read the full prescribing information for LETAIRIS.
- I agree to enroll in LEAP all patients prescribed LETAIRIS and re-enroll patients annually by completing the patient re-enrollment form.
- I will review the Medication Guide and Patient Enrollment Guide with each patient prior to prescribing LETAIRIS, and will discuss the risks of LETAIRIS, including the risk of teratogenicity, decreases in hemoglobin concentration and hematocrit, and the potential risk of reduced male fertility.
- I will determine if a woman is of childbearing potential* before enrolling her in LEAP. For women of childbearing potential I will order and review pregnancy tests prior to initiating treatment with LETAIRIS, and monthly during treatment in accordance with the LETAIRIS full prescribing information.
- For women of childbearing potential: I will educate and counsel them to use highly reliable contraception during LETAIRIS treatment and for one month after stopping treatment. If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS for pregnancy prevention, no additional contraception is needed. Women who do not choose one of these methods should always use two acceptable forms of contraception—one hormone method and one barrier method, or two barrier methods where one method is the male condom.
  - Acceptable hormone methods include: progesterone injectables, progesterone implants, combination oral contraceptives, transdermal patch, and vaginal ring.
  - Acceptable barrier methods include: diaphragm (with spermicide), cervical cap (with spermicide), and the male condom.
  - Partner's vasectomy must be used along with a hormone method or a barrier method.
  - All women of childbearing potential should undergo contraceptive counseling, with either the prescriber or another designated healthcare practitioner trained in contraceptive counseling.
  - Educate and counsel women of childbearing potential* on the use of emergency contraception in the event of unprotected sex or known or suspected contraceptive failure.
- I will counsel patients who fail to comply with the program requirements.
- I will notify LEAP of any adverse events, including death, or if any patient becomes pregnant during LETAIRIS treatment.

REQUIRED

Prescriber Signature: _____ Date: _____

Please visit **www.letairisrems.com** or call **1-866-664-LEAP (5327)** for more information about the LETAIRIS REMS program.

*See reverse side for definition of a woman of childbearing potential.

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Letairis® ambrisentan
5 mg and 10 mg Tablets

The prescriber must determine if a woman is of childbearing potential before enrolling her in LEAP.

- Women of childbearing potential must use highly reliable contraception during LETAIRIS treatment and for one month after stopping treatment.
  - If the patient has a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS for pregnancy prevention, no additional contraception is needed.
  - Women who do not choose one of these methods should always use two acceptable forms of contraception—one hormone method and one barrier method, or two barrier methods where one method is the male condom.
  - All women of childbearing potential should undergo contraceptive counseling, with either the prescriber or another designated healthcare practitioner trained in contraceptive counseling.
  - Educate and counsel women of childbearing potential on the use of emergency contraception in the event of unprotected sex or known or suspected contraceptive failure.

Acceptable Contraceptive Methods

Methods to Use by Themselves	Combination Methods	
	Hormone Methods Choose one and use with a barrier method	**Barrier Methods** Choose two OR choose one and use with a hormone method
Intrauterine devices (IUDs) • Copper T 380A IUD • LNg 20 IUS (progesterone IUD) **Tubal sterilization**	**Estrogen and progesterone** • Oral contraceptives • Transdermal patch • Vaginal ring **Progesterone only** • Injection • Implant	• Diaphragm with spermicide OR cervical cap with spermicide • Male condom (with or without spermicide)
	Partner's vasectomy must be used along with a hormone method or a barrier method.	

Definition of a Woman of Childbearing Potential

A woman of childbearing potential is a non-menopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This includes pubertal females who have not yet had a menses (premenarchal, Tanner Stage 3), perimenopausal women who have had a spontaneous menses in the last 12 months, and women who have had a tubal sterilization.

Pre-pubertal females (Tanner Stages 1 and 2) are not considered to be of childbearing potential. These patients should be carefully monitored for changes in childbearing potential status during LETAIRIS treatment. Notify LEAP if the patient's childbearing potential status changes.

Definition of Menopause

Menopause can be assumed to have occurred in a woman when there is either:

- Appropriate medical documentation of prior complete bilateral oophorectomy (i.e., surgical removal of the ovaries, resulting in "surgical menopause" and occurring at the age at which the procedure was performed), OR
- Permanent cessation of previously occurring menses as a result of ovarian failure with documentation of hormonal deficiency by a certified healthcare provider (i.e., "spontaneous menopause," which occurs in the United States at a mean age of 51.5 years).
  - Hormonal deficiency should be properly documented in the case of suspected spontaneous menopause as follows:
    - If age ≥54 years and with the absence of normal menses: Serum follicle stimulating hormone (FSH) level elevated to within the post-menopausal range based on the laboratory reference range where the hormonal assay is performed;
    - If age <54 years and with the absence of normal menses: Negative serum or urine human chorionic gonadotropin (hCG) with concurrently elevated serum FSH level in the post-menopausal range, depressed estradiol (E2) level in the post-menopausal range, and absent serum progesterone level, based on the laboratory reference ranges where the hormonal assays are performed.

This form is part of an FDA approved REMS.
There is no need to fax this side of the form.

Please see the accompanying patient Medication Guide and full prescribing information, including **boxed WARNING**.

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Important Safety Information

BOXED WARNING: CONTRAINDICATED IN PREGNANCY

Do not administer LETAIRIS to a pregnant woman because it may cause fetal harm. LETAIRIS is very likely to produce serious birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals *[see Contraindications]*.

Pregnancy must therefore be excluded before the initiation of treatment with LETAIRIS and prevented during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS, in which case no additional contraception is needed. Obtain monthly pregnancy tests *[see Warnings and Precautions]*.

Because of the risk of birth defects, LETAIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the LETAIRIS Education and Access Program (LEAP). As a component of the LETAIRIS REMS, prescribers, patients, and pharmacies must enroll in the program *[see Warnings and Precautions]*.

Please visit www.letairisrems.com or call 1-866-664-LEAP (5327) for more information about the LETAIRIS REMS program.

Please see the accompanying patient Medication Guide and full prescribing information, including **boxed WARNING**, for more complete information.

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LETAIRIS EDUCATION AND ACCESS PROGRAM (LEAP)

Prescriber Guide: LETAIRIS and the LEAP Program

This guide is part of an FDA approved REMS.

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LETAIRIS and the LEAP Program

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. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%).

LETAIRIS is contraindicated in women who are or may become pregnant, as LETAIRIS may cause fetal harm when administered to a pregnant woman.

Because of the risk of birth defects, LETAIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the LETAIRIS Education and Access Program (LEAP). This program helps ensure the benefits of LETAIRIS outweigh the risks, including the risk of serious birth defects.

LETAIRIS may be prescribed only through LEAP. As a component of LEAP, prescribers, patients, and pharmacies must fulfill these required components of LEAP:

- Healthcare professionals who prescribe LETAIRIS must complete the LEAP Prescriber Enrollment and Agreement Form, enroll in the program, and comply with the REMS requirements
- All patients must be enrolled in LEAP, using the LEAP Patient Enrollment and Consent Form, and re-enrolled annually by their prescribing healthcare professional
- For women of childbearing potential: (1) a pregnancy test must be ordered and reviewed by the prescriber prior to initiation of LETAIRIS treatment and monthly during treatment; (2) she must agree to be contacted prior to each shipment to confirm that a pregnancy test was completed; (3) she must agree to be counseled on the requirements of the REMS program and the risks of LETAIRIS; and (4) she must agree to be contacted by Gilead if she becomes pregnant while on LETAIRIS or within 30 days of treatment discontinuation
- Pharmacies that dispense LETAIRIS must enroll in the program and agree to comply with the REMS requirements

Further information is available at **www.letairisrems.com** or **1-866-664-LEAP (5327)**.

Overview of LEAP Roles and Responsibilities

The Prescriber:

- Reads the LETAIRIS full prescribing information and understands the risks of LETAIRIS
- Completes a Prescriber Enrollment and Agreement Form and faxes it to LEAP
- Advises the patient that LETAIRIS is only available through a restricted distribution program called LEAP
- Educates the patient about the risks of LETAIRIS using the LETAIRIS Medication Guide and Patient Enrollment Guide before initiating LETAIRIS treatment, and provides the patient with copies
- Educates and counsels women of childbearing potential* on the need to use highly reliable contraception during treatment and for 1 month after stopping treatment, and on the use of emergency contraception in the event of unprotected sex or known or suspected contraception failure
  - Refer to pages 6 and 7 for information on women of childbearing potential and acceptable forms of contraception
- Orders and reviews pregnancy tests (for women of childbearing potential) prior to initiating treatment and monthly during treatment
- Orders and reviews hemoglobin concentrations and hematocrit prior to initiating treatment with LETAIRIS, at 1 month, and periodically thereafter
- Completes a Patient Enrollment and Consent Form completely and legibly
  - Confirm patient has agreed to comply with program requirements and has signed the form where indicated
  - As the prescriber, sign the completed form. Fax the completed form, along with all patient insurance information, including prescription drug benefits and medical benefits, to **1-888-882-4035**
  - Keep the original form with the patient's records
- Re-enrolls patients annually. You will be reminded when re-enrollment is required
- Counsels patients who fail to comply with the program requirements and notifies LEAP of any adverse events, including death, or if any patient becomes pregnant during LETAIRIS treatment

*The prescriber must determine if a woman is of childbearing potential before enrolling her in LEAP.

The LEAP Coordinating Center:

- Enters every LETAIRIS prescriber and patient in the LEAP database
- Works with the Certified Specialty Pharmacy to confirm insurance coverage or investigates alternative sources of reimbursement or assistance
- Sends patient information to the chosen Certified Specialty Pharmacy

The Certified Specialty Pharmacy:

- Files the insurance claim
- Contacts all women of childbearing potential receiving LETAIRIS each month to confirm completion of pregnancy testing and counsel on the risk of teratogenicity
- Contacts all patients to make sure they will be available to receive their LETAIRIS shipment
- Provides a copy of the Medication Guide to patients or caregivers each time LETAIRIS is dispensed and instructs patients to read it each time they receive LETAIRIS
- Answers questions and provides information about LETAIRIS
- Ships LETAIRIS to the patient

Participating Certified Specialty Pharmacies

LETAIRIS can only be supplied through Certified Specialty Pharmacies. For a list of participating Certified Specialty Pharmacies, visit **www.letairisrems.com**.

Treating Women of Childbearing Potential

Definition of a Woman of Childbearing Potential

A woman of childbearing potential is a non-menopausal woman who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This includes pubertal women who have not yet had a menses (premenarchal, Tanner Stage 3), perimenopausal women who have had a spontaneous menses in the last 12 months, and women who have had a tubal sterilization.

Pre-pubertal women (Tanner Stages 1 and 2) are not considered to be of childbearing potential. These patients should be carefully monitored for changes in childbearing potential status during LETAIRIS treatment. Notify LEAP if the patient's childbearing potential status changes.

Definition of Menopause

Menopause can be assumed to have occurred in a woman when there is either:

- Appropriate medical documentation of prior complete bilateral oophorectomy (i.e., surgical removal of the ovaries, resulting in "surgical menopause" and occurring at the age at which the procedure was performed), OR
- Permanent cessation of previously occurring menses as a result of ovarian failure with documentation of hormonal deficiency by a certified healthcare provider (i.e., "spontaneous menopause," which occurs in the United States at a mean age of 51.5 years)
  - Hormonal deficiency should be properly documented in the case of suspected spontaneous menopause as follows:
    - If age ≥54 years and with the absence of normal menses: serum follicle stimulating hormone (FSH) level elevated to within the post-menopausal range based on the laboratory reference range where the hormonal assay is performed
    - If age <54 years and with the absence of normal menses: negative serum or urine human chorionic gonadotropin (hCG) with concurrently elevated serum FSH level in the post-menopausal range, depressed estradiol (E2) level in the post-menopausal range, and absent serum progesterone level, based on the laboratory reference ranges where the hormonal assays are performed

Acceptable Contraceptive Methods

Methods to Use by Themselves	Combination Methods	
	Hormone Methods Choose one and use with a barrier method	**Barrier Methods** Choose two OR choose one and use with a hormone method
Intrauterine devices (IUDs) • Copper T 380A IUD • LNg 20 IUS (progesterone IUD) **Tubal sterilization**	**Estrogen and progesterone** • Oral contraceptives • Transdermal patch • Vaginal ring **Progesterone only** • Injection • Implant	• Diaphragm with spermicide OR cervical cap with spermicide • Male condom (with or without spermicide)
	Partner's vasectomy must be used along with a hormone method or a barrier method.	

  - If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS for pregnancy prevention, no additional contraception is needed
  - Women who do not choose one of these methods should always use two acceptable forms of contraception—one hormone method and one barrier method, or two barrier methods where one method is the male condom. Please refer to the table above for a complete list of acceptable contraceptive methods. A similar table also appears in the Patient Enrollment Guide and should be used to discuss reliable birth control with patients
  - All women of childbearing potential should undergo contraceptive counseling with either the prescriber or another designated healthcare practitioner trained in contraceptive counseling
  - Educate and counsel women of childbearing potential on the use of emergency contraception in the event of unprotected sex or known or suspected contraceptive failure
  - If pregnancy is suspected for any reason, a pregnancy test must be performed. **The prescriber must notify LEAP of any pregnancies that occur during treatment or within 30 days of discontinuation**

LETAIRIS Risk Information

Education is a key component of risk management. Prescribers must review the LETAIRIS full prescribing information to prepare for patient counseling. This guide is only a summary of some of the important information about LETAIRIS.

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. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%).

Risk of Teratogenicity

LETAIRIS may cause fetal harm when administered to a pregnant woman. Pregnancy must be excluded prior to the initiation of LETAIRIS treatment and prevented thereafter.

Women of childbearing potential must agree to the following:

- A negative pregnancy test prior to treatment initiation is required
- Monthly pregnancy testing during LETAIRIS treatment and 1 month after stopping treatment
- Use of highly reliable contraception during LETAIRIS treatment and for 1 month after stopping treatment
  - If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS for pregnancy prevention, no additional contraception is needed
  - Women who do not choose one of these methods should always use two acceptable forms of contraception—one hormone method and one barrier method, or two barrier methods where one method is the male condom. Refer to page 7 for a complete list of acceptable contraception methods
- Undergo contraceptive counseling with either the prescriber or another designated healthcare practitioner trained in contraceptive counseling
- Report any delay in onset of menses, or any other reason to suspect pregnancy during treatment, to the prescriber immediately

If pregnancy is suspected for any reason, a pregnancy test must be performed. If the pregnancy test is positive, the prescriber and patient should discuss the risk of pregnancy, the potential risk to the fetus, and the patient's options. The prescriber must notify LEAP of any pregnancies that occur during treatment or within 30 days of discontinuation.

There are no data regarding the use of LETAIRIS in pregnant women.

WHO=World Health Organization.

Please see the accompanying patient Medication Guide and full prescribing information, including **boxed WARNING**, for more complete information.

LETAIRIS Risk Information

Fluid Retention

Peripheral edema is a known class effect of ERAs, and is also a clinical consequence of PAH and worsening PAH. In the placebo-controlled studies, there was an increased incidence of peripheral edema in patients treated with doses of 5 or 10 mg LETAIRIS compared with placebo (see Adverse Reactions on next page). Most edema was mild to moderate in severity, and it occurred with greater frequency and severity in elderly patients.

In addition, there have been postmarketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting LETAIRIS. Patients required intervention with a diuretic, fluid management, or, in some cases, hospitalization for decompensating heart failure.

If clinically significant fluid retention develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as LETAIRIS or underlying heart failure, and the possible need for specific treatment or discontinuation of LETAIRIS therapy.

Pulmonary Veno-occlusive Disease

If patients develop acute pulmonary edema during initiation of therapy with vasodilating agents such as LETAIRIS, underlying pulmonary veno-occlusive disease should be considered, and if confirmed, LETAIRIS should be discontinued.

Potential Risk of Reduced Male Fertility

In a 6-month study of another ERA, bosentan, 25 male patients with WHO functional class III and IV PAH and normal baseline sperm count were evaluated for effects on testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with bosentan. One patient developed marked oligospermia at 3 months and the sperm count remained low with two follow-up measurements over the subsequent 6 weeks. Bosentan was discontinued and after 2 months the sperm count had returned to baseline levels. In 22 patients who completed 6 months of treatment, sperm count remained within the normal range and no changes in sperm morphology, sperm motility, or hormone levels were observed. Based on these findings and preclinical data from ERAs, it cannot be excluded that ERAs such as LETAIRIS have an adverse effect on spermatogenesis.

Decreases in Hemoglobin Concentration and Hematocrit

Decreases in hemoglobin concentration and hematocrit have followed administration of other ERAs and were observed in clinical studies with LETAIRIS. These decreases were observed within the first few weeks of treatment with LETAIRIS, and may persist during treatment. There have been postmarketing reports of anemia requiring transfusion.

Measure hemoglobin prior to initiation of LETAIRIS, at 1 month, and periodically thereafter. Initiation of LETAIRIS therapy is not recommended for patients with clinically significant anemia. If a clinically significant decrease in hemoglobin is observed and other causes have been excluded, consider discontinuing LETAIRIS.

Adverse Reactions

Placebo-adjusted adverse reactions in Phase III clinical trials occurring in >3% of patients receiving LETAIRIS compared with patients receiving placebo were peripheral edema, nasal congestion, sinusitis, and flushing. Most adverse drug reactions were mild to moderate and only nasal congestion was dose-dependent.

Please see the accompanying patient Medication Guide and full prescribing information, including **boxed WARNING**, for more complete information.

Important Safety Information

BOXED WARNING: CONTRAINDICATED IN PREGNANCY

Do not administer LETAIRIS to a pregnant woman because it may cause fetal harm. LETAIRIS is very likely to produce serious birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals *[see Contraindications]*.

Pregnancy must therefore be excluded before the initiation of treatment with LETAIRIS and prevented during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS, in which case no additional contraception is needed. Obtain monthly pregnancy tests *[see Warnings and Precautions]*.

Because of the risk of birth defects, LETAIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the LETAIRIS Education and Access Program (LEAP). As a component of the LETAIRIS REMS, prescribers, patients, and pharmacies must enroll in the program *[see Warnings and Precautions]*.

Please see the accompanying patient Medication Guide. The patient Medication Guide summarizes important information about LETAIRIS. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider for information about LETAIRIS that is written for health professionals.

GILEAD

Letairis®
ambrisentan
5 mg and 10 mg Tablets

Reference ID: 3088104

LETAIRIS EDUCATION AND ACCESS PROGRAM (LEAP)

Patient Enrollment Guide

For starting therapy with LETAIRIS

This guide is part of an FDA approved REMS.

Letairis®
ambrisentan
5 mg and 10 mg Tablets

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Information for all patients on LETAIRIS

What is LETAIRIS?

LETAIRIS is a prescription medicine to treat pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of your lungs. LETAIRIS can improve your ability to exercise and it can help slow down the worsening of your physical condition and symptoms.

What are the serious risks of LETAIRIS?

LETAIRIS can cause serious birth defects if taken during pregnancy. Women must not be pregnant when they start taking LETAIRIS or become pregnant during treatment. Other risks include low red blood cell levels (anemia), sperm count reduction, and swelling all over the body.

What is the LETAIRIS Education and Access Program (LEAP)?

LETAIRIS is available only through a restricted program called the LETAIRIS Education and Access Program (LEAP).

In order for you to receive LETAIRIS:

1) You must talk with your doctor to ensure the benefits outweigh the risks of LETAIRIS
2) You must agree to all of the instructions in LEAP
3) Your doctor will enroll you in LEAP
4) Your prescription will be mailed to you from a Certified Specialty Pharmacy that you and your doctor will choose

How do I enroll in LEAP?

Enrolling in LEAP is easy. Follow these steps with your doctor:

- Read all the patient information about LETAIRIS and LEAP
- Talk with your doctor to ensure the benefits outweigh the risks of LETAIRIS
- Ask questions. Make sure you understand what you need to do
- You and your doctor choose a Certified Specialty Pharmacy to supply LETAIRIS. In some cases your insurance company may require you to use a specific Certified Specialty Pharmacy
- Your doctor fills out the enrollment form. After you read and sign it, your doctor sends it to LEAP

What tests do I need to have for LEAP?

If you are a woman who can get pregnant, you must:

- Have a negative pregnancy test before you start taking LETAIRIS and before you receive your refills. **See page 6 of this guide for more information**
- **Be sure to complete your monthly pregnancy test as your doctor orders for you. You may not receive your LETAIRIS refill on time if you do not complete this test**

All patients may have the following test conducted as part of LETAIRIS therapy:

- A blood test to check your red blood cells. Low red blood cell levels (anemia) can happen after starting LETAIRIS, sometimes requiring blood transfusions. This test may be repeated during your treatment with LETAIRIS

Certified Specialty Pharmacies

Certified Specialty Pharmacies provide products and services for patients with certain diseases. Only Certified Specialty Pharmacies carry LETAIRIS. In some cases your insurance company may require you to use a specific Certified Specialty Pharmacy.

Your Certified Specialty Pharmacy ships your LETAIRIS refill to you. Before each shipment, you will be called to make sure you will be available to receive your LETAIRIS shipment. If you are a woman who is able to become pregnant, your Certified Specialty Pharmacy will confirm that you have completed monthly pregnancy testing before refilling your prescription. It is important that your Certified Specialty Pharmacy is able to contact you in order to avoid delays in your refills.

Your Certified Specialty Pharmacy will:

- File your insurance claims
- Resolve insurance problems
- Refill your prescription
- Answer questions and provide information about LETAIRIS
- Ship your medicine

Participating Certified Specialty Pharmacies

For a list of participating Certified Specialty Pharmacies, visit **www.letairisrems.com**.

If you have questions or concerns about LETAIRIS, talk to your doctor. Please visit **www.letairisrems.com** or call **1-866-664-LEAP (5327)** for more information about LEAP.

Information for women who are able to get pregnant

Letairis® ambrisentan
5 mg and 10 mg Tablets

Special information

You are considered a woman who is able to get pregnant if you have had a period in the past year or have not gone through menopause. LETAIRIS can cause serious birth defects if taken during pregnancy. Women must not be pregnant when they start taking LETAIRIS or become pregnant during treatment.

Women who are able to get pregnant must have a negative pregnancy test before beginning treatment with LETAIRIS and each month during treatment. Your doctor will decide when to do the test, depending on your menstrual cycle.

To receive LETAIRIS you must:

- Have monthly pregnancy tests. Your doctor orders the tests and your Certified Specialty Pharmacy will call you and ask whether you have completed this test before shipping your refill
- Use birth control during your LETAIRIS treatment and for 1 month after stopping your LETAIRIS treatment

Your birth control options

Your doctor will talk to you about LEAP and your birth control options. Use the table below to help decide what birth control options are best for you.

You may choose:

1) One method from the first column to use by itself

Or

2) Two other methods used together each time you have intercourse

Acceptable Birth Control Methods

Methods to Use by Themselves	Combination Methods	
	Hormone Methods Choose one and use with a barrier method	**Barrier Methods** Use two OR choose one and use with a hormone method
Intrauterine devices (IUDs) • Copper T 380A IUD • LNg 20 IUS (progesterone IUD) **Tubal sterilization**	**Estrogen and progesterone** • Oral contraceptives • Transdermal patch • Vaginal ring **Progesterone only** • Injection • Implant	• Diaphragm with spermicide OR cervical cap with spermicide • Male condom (with or without spermicide)
	Partner's vasectomy must be used along with a hormone method or a barrier method.	

Do not have unprotected sex. Talk to your doctor or pharmacist right away if you have unprotected sex or if you think your birth control has failed. Your doctor may tell you to use emergency birth control. Tell your doctor right away if you miss a menstrual period or if you think you may be pregnant.

Please visit **www.letairisrems.com** or call **1-866-664-LEAP (5327)** for more information about LEAP.

LEAP LETAIRIS Education and Access Program (LEAP)

Ongoing Education Program

Gilead Sciences, Inc. is providing you LETAIRIS Education and Access Program (LEAP) materials to support your understanding of the program and the risks of LETAIRIS therapy. The materials provided may reflect updates to the LEAP program, program materials, or the full prescribing information (PI) for LETAIRIS.

Enclosed you will find:

- LEAP Prescriber Guide: LETAIRIS and the LEAP Program
- LEAP Patient Enrollment Guide
- LETAIRIS PI and Patient Medication Guide

As a LETAIRIS prescriber, it is important that you review the enclosed materials, and sign and return the Ongoing Education Program form to 1-888-882-4035 to confirm receipt of these education materials, your understanding of LEAP requirements, and the risks of LETAIRIS.

Prescriber Information

First Name: _____ Middle Initial: ____ Last Name: _____ Suffix: _____

Specialty: _____ Name of Facility: _____ Office Contact: _____

Address: _____ City: _____ State: _____ ZIP: _____

E-mail: _____ Phone: (____) _____ Fax: (____) _____

State License No.: _____ NPI No.: _____ DEA No.: _____

Prescriber Agreement

By signing below, I acknowledge: (1) that I have reviewed and discussed with my patients prior to enrollment and initiation of LETAIRIS treatment the Medication Guide and Patient Enrollment Guide and the risks of LETAIRIS (including teratogenicity, decreases in hemoglobin concentration and hematocrit, and the potential risk of reduced male fertility); (2) that I will review these LEAP materials with my patients on an annual basis; and (3) that I understand the risks of LETAIRIS treatment and my obligation as a LETAIRIS prescriber to educate my patients about the risks, counsel them on risk reduction, monitor them to assure safe use, renew my patients' prescriptions and re-enroll them in LEAP on an annual basis, counsel patients who fail to comply with the program requirements, and report any adverse events to LEAP during the treatment with LETAIRIS, as required by the LEAP program.

REQUIRED
Prescriber Signature: _____ Date: _____

Fax: 1-888-882-4035

Please visit **www.letairisrems.com** or call **1-866-664-LEAP (5327)** for more information about the LETAIRIS REMS program.

This form is part of an FDA approved REMS.

GILEAD

Reference ID: 3088104 Printed on recycled paper.

Letairis® isentan
5 mg and 10 mg Tablets

LEAP Ongoing Education

LETAIRIS Education and Access Program (LEAP) Patient Enrollment and Consent Form

Select a preferred Certified Specialty Pharmacy:

☐ Accredo ☐ Aetna Specialty Pharmacy ☐ CIGNA Tel-Drug ☐ CuraScript ☐ CVS Caremark

☐ Kaiser Specialty Pharmacy ☐ Walgreens Specialty Pharmacy ☐ WellCare Specialty Pharmacy

Patient Information (PLEASE PRINT)

First Name: _____ Middle Initial: _____ Last Name: _____

Address: _____ City: _____ State: _____ ZIP: _____

Birthdate: ____ /____ /____ Gender: ☐ M ☐ F Preferred Time to Contact: ☐ Day ☐ Evening

Preferred Phone: (____)_____ Alternate Phone: (____)_____ E-mail: _____

Alternate Contact Name: _____ Phone: (____)_____ Relationship: _____

I acknowledge that I have read the Medication Guide and Patient Enrollment Guide and that I have been informed about the risks of Letairis® (ambrisentan), including serious birth defects, low red blood cell count, and low sperm count.

For women who may become pregnant: I agree to have the required monthly pregnancy tests. I acknowledge that I will be contacted by Gilead and/or its agents and contractors to receive counseling on the serious risk of birth defects, to ensure that I have completed the required pregnancy testing before I receive my LETAIRIS refill, and, if I become pregnant, to obtain information about my pregnancy.

REQUIRED
Patient/Guardian Signature: _____ Date: _____

I authorize my healthcare providers and health plans to disclose personal and medical information about me to Gilead and its agents and contractors ("Gilead") and I authorize Gilead to use and disclose this information to: 1) establish my benefit eligibility, including benefit eligibility for laboratory services; 2) communicate with my healthcare providers and health plans about my medical care; 3) provide support services, including facilitating the provision of LETAIRIS to me and facilitating laboratory testing on my behalf; and 4) evaluate the safety and overall effectiveness of Gilead's education program, the LEAP program, as well as the safety and efficacy of LETAIRIS. I agree that using the contact information I provide, Gilead may get in touch with me for reasons related to the LEAP program and may leave messages for me that disclose that I take LETAIRIS.

I understand that once my health information has been disclosed to Gilead, privacy laws may no longer restrict its use or disclosure; however, Gilead agrees to protect my information by using and disclosing it only for the purposes described above or as required by law. I further understand I may refuse to sign this authorization and that if I refuse, my eligibility for health plan benefits and treatment by my doctor will not change, but I will not have access to the LETAIRIS support services described herein. I may also cancel this authorization in the future by notifying Gilead in writing and submitting it by fax to 1-888-882-4035 or by calling 1-866-664-LEAP (5327). If I cancel, Gilead will stop using or disclosing my information for the purposes listed above, except as required by law or as necessary for the orderly termination of my participation in LEAP. I am entitled to a copy of this signed authorization, which expires 10 years from the date it is signed by me.

REQUIRED
Patient/Guardian Signature: _____ Date: _____

Prescriber Information (PLEASE PRINT) Office Contact and E-mail Address: _____

First Name: _____ Last Name: _____ State License #: _____

Address: _____ City: _____ State: _____ ZIP: _____

Phone: (____)_____ Fax: (____)_____ NPI #: _____ DEA #: _____

Prescription: LETAIRIS: ☐ 5 mg tablets (30 tablets) Refills: ____ ☐ 10 mg tablets (30 tablets) Refills: ____ ☐ PO ☐ QD

Instructions: _____

Ship to: ☐ Patient Home (address listed above) ☐ Prescriber Office (address listed above) ☐ Other: (please indicate below)

Name: _____ Address: _____

City: _____ State: _____ ZIP: _____ Phone: (____)_____

For women only, please indicate whether this patient is of childbearing potential: ☐ Yes ☐ No
(Please note that women who have had a tubal sterilization are considered to be of childbearing potential.)
– If yes, has a negative pre-LETAIRIS pregnancy test been confirmed? ☐ Yes ☐ No

Statement of Medical Necessity (This is for insurance purposes only, not to suggest approved uses or indications.)

Diagnosis: Pulmonary Arterial Hypertension (Please select one category below)

☐ Familial (ICD 416.0) ☐ Idiopathic (ICD 416.0) ☐ Scleroderma (ICD 710.1) ☐ HIV (ICD 042 _____) ☐ Lupus (ICD 710.0)

☐ Portal Hypertension (ICD 572.3) ☐ Congenital Heart Defects (ICD 745. _____) ☐ Other: _____ (ICD _____)

By signing, I certify that the above therapy is medically necessary. I have reviewed the Medication Guide and Patient Enrollment Guide with the patient and have counseled the patient on the risks of LETAIRIS, including teratogenicity, decreases in hemoglobin concentration and hematocrit, and the potential risk of reduced male fertility. I will order and review pregnancy tests (for women of childbearing potential) prior to initiation of LETAIRIS treatment, and monthly during treatment in accordance with the LETAIRIS full prescribing information.

REQUIRED
Prescriber Signature: _____ Date: _____

Fax this enrollment form and all patient insurance information, including drug benefit cards (front and back) to 1 888 882 4035.

LETAIRIS Education and Access Program (LEAP)
Instructions

The LETAIRIS Education and Access Program (LEAP) is a restricted program to help prescribers and patients learn about the risks of Letairis® (ambrisentan). To minimize the risk of fetal exposure and adverse fetal outcomes in women of childbearing potential, LETAIRIS is available only through LEAP.

Please complete the following steps prior to faxing the patient enrollment form.

Step 1:	**Check the box** that indicates the patient's preferred Certified Specialty Pharmacy.
Step 2:	**Complete** Patient Information section, including the best method for LEAP to contact your patient.
Step 3:	**Obtain first patient signature.** This is to confirm that the patient has read the LETAIRIS patient Medication Guide and has been informed of the risks of LETAIRIS.
Step 4:	**Obtain second patient signature**. Two signatures are required from the patient. The second is for HIPAA release.
Step 5:	**Complete** Prescriber Information section, including office contact for additional questions regarding this application.
Step 6:	**Complete** Prescription section.
Step 7:	**Provide your signature** on the Prescriber Signature line.

Fax completed form and copies of all relevant insurance information (medical and prescription drug benefits) to **LEAP** at **1-888-882-4035**.

Please visit **www.letairisrems.com** or call **1-866-664-LEAP (5327)** for more information about the LETAIRIS REMS program.

Please see the accompanying patient Medication Guide and full prescribing information, including **boxed WARNING**.

This form is part of an FDA approved REMS.

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LETAIRIS Education and Access Program (LEAP) and *LabSync* Patient Enrollment and Consent Form

Enroll Patient in *LabSync*®: ☐ Yes ☐ No

Select a preferred Certified Specialty Pharmacy:

☐ Accredo ☐ Aetna Specialty Pharmacy ☐ CIGNA Tel-Drug ☐ CuraScript ☐ CVS Caremark

☐ Kaiser Specialty Pharmacy ☐ Walgreens Specialty Pharmacy ☐ WellCare Specialty Pharmacy

Patient Information (PLEASE PRINT)

First Name: _____ Middle Initial: _____ Last Name: _____

Address: _____ City: _____ State: _____ ZIP: _____

Birthdate: ____ /____ /____ Gender: ☐ M ☐ F Preferred Time to Contact: ☐ Day ☐ Evening

Preferred Phone: (____)_____ Alternate Phone: (____)_____ E-mail: _____

Alternate Contact Name: _____ Phone: (____)_____ Relationship: _____

I acknowledge that I have read the Medication Guide and Patient Enrollment Guide and that I have been informed about the risks of Letairis® (ambrisentan), including serious birth defects, low red blood cell count, and low sperm count.

For women who may become pregnant: I agree to have the required monthly pregnancy tests. I acknowledge that I will be contacted by Gilead and/or its agents and contractors to receive counseling on the serious risk of birth defects, to ensure that I have completed the required pregnancy testing before I receive my LETAIRIS refill, and, if I become pregnant, to obtain information about my pregnancy.

REQUIRED
Patient/Guardian Signature: _____ Date: _____

I authorize my healthcare providers and health plans to disclose personal and medical information about me to Gilead and its agents and contractors ("Gilead") and I authorize Gilead to use and disclose this information to: 1) establish my benefit eligibility, including benefit eligibility for laboratory services; 2) communicate with my healthcare providers and health plans about my medical care; 3) provide support services, including facilitating the provision of LETAIRIS to me and facilitating laboratory testing on my behalf; and 4) evaluate the safety and overall effectiveness of Gilead's education program, the LEAP and *LabSync* programs, as well as the safety and efficacy of LETAIRIS. I agree that using the contact information I provide, Gilead may get in touch with me for reasons related to the LEAP and *LabSync* programs and may leave messages for me that disclose that I take LETAIRIS. Additionally, I understand that I may choose not to participate in *LabSync*, but I am still eligible to participate in LEAP.

I understand that once my health information has been disclosed to Gilead, privacy laws may no longer restrict its use or disclosure; however, Gilead agrees to protect my information by using and disclosing it only for the purposes described above or as required by law. I further understand I may refuse to sign this authorization and that if I refuse, my eligibility for health plan benefits and treatment by my doctor will not change, but I will not have access to the LETAIRIS support services described herein. I may also cancel this authorization in the future by notifying Gilead in writing and submitting it by fax to 1-888-882-4035 or by calling 1-866-664-LEAP (5327). If I cancel, Gilead will stop using or disclosing my information for the purposes listed above, except as required by law or as necessary for the orderly termination of my participation in LEAP. I am entitled to a copy of this signed authorization, which expires 10 years from the date it is signed by me.

REQUIRED
Patient/Guardian Signature: _____ Date: _____

Prescriber Information (PLEASE PRINT) Office Contact and E-mail Address: _____

First Name: _____ Last Name: _____ State License #: _____

Address: _____ City: _____ State: _____ ZIP: _____

Phone: (____)_____ Fax: (____)_____ NPI #: _____ DEA #: _____

Prescription: LETAIRIS: ☐ 5 mg tablets (30 tablets) Refills: ____ ☐ 10 mg tablets (30 tablets) Refills: ____ ☐ PO ☐ QD

Instructions: _____

Ship to: ☐ Patient Home (address listed above) ☐ Prescriber Office (address listed above) ☐ Other: (please indicate below)

Name: _____ Address: _____

City: _____ State: _____ ZIP: _____ Phone: (____)_____

For women only, please indicate whether this patient is of childbearing potential: ☐ Yes ☐ No
(Please note that women who have had a tubal sterilization are considered to be of childbearing potential.)
– If yes, has a negative pre-LETAIRIS pregnancy test been confirmed? ☐ Yes ☐ No

Statement of Medical Necessity (This is for insurance purposes only, not to suggest approved uses or indications.)

Diagnosis: Pulmonary Arterial Hypertension (Please select one category below)

☐ Familial (ICD 416.0) ☐ Idiopathic (ICD 416.0) ☐ Scleroderma (ICD 710.1) ☐ HIV (ICD 042 _____) ☐ Lupus (ICD 710.0)

☐ Portal Hypertension (ICD 572.3) ☐ Congenital Heart Defects (ICD 745. _____) ☐ Other: _____ (ICD _____)

By signing, I certify that the above therapy is medically necessary. I have reviewed the Medication Guide and Patient Enrollment Guide with the patient and have counseled the patient on the risks of LETAIRIS, including teratogenicity, decreases in hemoglobin concentration and hematocrit, and the potential risk of reduced male fertility. I will order and review pregnancy tests (for women of childbearing potential) prior to initiation of LETAIRIS treatment, and monthly during treatment in accordance with the LETAIRIS full prescribing information. I authorize *LabSync* to order laboratory tests and receive laboratory results on my behalf for patients enrolled in LEAP and *LabSync*.

REQUIRED
Prescriber Signature: _____ Date: _____

Fax this enrollment form and all patient insurance information, including drug benefit cards (front and back) to 1 888 882 4035.

ILEAD

Please visit **www.letairisrems.com** or call **1-866-664-LEAP (5327)** for more information about the LETAIRIS REMS program.

LETAIRIS Education and Access Program (LEAP)
Instructions

The LETAIRIS Education and Access Program (LEAP) is a restricted program to help prescribers and patients learn about the risks of Letairis® (ambrisentan). To minimize the risk of fetal exposure and adverse fetal outcomes in women of childbearing potential, LETAIRIS is available only through LEAP.

Please complete the following steps prior to faxing the patient enrollment form.

Step 1:	**Check "Yes" or "No"** to indicate whether patient will participate in *LabSync*®.
Step 2:	**Check the box** that indicates the patient's preferred Certified Specialty Pharmacy.
Step 3:	**Complete** Patient Information section, including the best method for LEAP to contact your patient.
Step 4:	**Obtain first patient signature.** This is to confirm that the patient has read the LETAIRIS patient Medication Guide and has been informed of the risks of LETAIRIS.
Step 5:	**Obtain second patient signature.** Two signatures are required from the patient. The second is for HIPAA release.
Step 6:	**Complete** Prescriber Information section, including office contact for additional questions regarding this application.
Step 7:	**Complete** Prescription section.
Step 8:	**Provide your signature** on the Prescriber Signature line.

Fax completed form and copies of all relevant insurance information (medical and prescription drug benefits) to **LEAP** at **1-888-882-4035**.

Please visit **www.letairisrems.com** or call **1-866-664-LEAP (5327)** for more information about the LETAIRIS REMS program.

Please see the accompanying patient Medication Guide and full prescribing information, including **boxed WARNING**.

This form is part of an FDA approved REMS.

GILEAD

FOR V.A. USE ONLY

LETAIRIS Education and Access Program (LEAP) Patient Enrollment and Consent Form

Certified Specialty Pharmacy: ☐ Accredo

Patient Information (PLEASE PRINT)

First Name: _____ Middle Initial: _____ Last Name: _____

Address: _____ City: _____ State: _____ ZIP: _____

Birthdate: ____ /____ /____ Gender: ☐ M ☐ F Preferred Time to Contact: ☐ Day ☐ Evening

Preferred Phone: (____)_____ Alternate Phone: (____)_____ E-mail: _____

Alternate Contact Name: _____ Phone: (____)_____ Relationship: _____

I acknowledge that I have read the Medication Guide and Patient Enrollment Guide and that I have been informed about the risks of Letairis® (ambrisentan), including serious birth defects, low red blood cell count, and low sperm count.

For women who may become pregnant: I agree to have the required monthly pregnancy tests. I acknowledge that I will be contacted by Gilead and/or its agents and contractors to receive counseling on the serious risk of birth defects, to ensure that I have completed the required pregnancy testing before I receive my LETAIRIS refill, and, if I become pregnant, to obtain information about my pregnancy.

REQUIRED
Patient/Guardian Signature: _____ Date: _____

I authorize Veterans Health Care Administration ("VA"), my specialty pharmacy or pharmacies, and my health plans to disclose personal and medical information about me to LEAP, which is run by Gilead and its agents and contractors ("LEAP"). I authorize LEAP to use and disclose this information to: 1) establish my eligibility for benefits; 2) communicate with my healthcare providers and health plans about my medical care; 3) provide LETAIRIS support services, including facilitating the provision of LETAIRIS to me; and 4) evaluate the effectiveness of Gilead's education programs. I agree that using the contact information I provide, LEAP may get in touch with me for reasons related to LEAP and may leave messages for me that disclose that I take LETAIRIS.

I understand that once my health information has been disclosed to LEAP, privacy laws may no longer restrict its use or disclosure; however, LEAP agrees to use and disclose the information only as permitted in this authorization or as required by law. I further understand I may refuse to sign this authorization and that if I refuse, my eligibility for health plan benefits and treatment by my doctor will not change, but I will not be eligible to receive LETAIRIS since, as a result of not signing, I will not have access to the FDA-required LETAIRIS support services described herein. I may also cancel this authorization in the future by notifying LEAP in writing and submitting it by fax to 1-888-882-4035 or by calling 1-866-664-LEAP (5327). If I cancel this authorization, LEAP will stop using or disclosing my information for the purposes listed above, except as required by law or as necessary for the orderly termination of my participation in LEAP. I am entitled to a copy of this signed authorization, which expires 10 years from the date it is signed by me.

REQUIRED
Patient/Guardian Signature: _____ Date: _____

Prescriber Information (PLEASE PRINT) Office Contact and E-mail Address: _____

First Name: _____ Last Name: _____ State License #: _____

Address: _____ City: _____ State: _____ ZIP: _____

Phone: (____)_____ Fax: (____)_____ NPI #: _____ DEA #: _____

Prescription: LETAIRIS: ☐ 5 mg tablets (30 tablets) Refills: ____ ☐ 10 mg tablets (30 tablets) Refills: ____ ☐ PO ☐ QD

Instructions: _____

Ship to: ☐ Patient Home (address listed above) ☐ Prescriber Office (address listed above) ☐ Other: (please indicate below)

Name: _____ Address: _____

City: _____ State: _____ ZIP: _____ Phone: (____)_____

For women only, please indicate whether this patient is of childbearing potential: ☐ Yes ☐ No
(Please note that women who have had a tubal sterilization are considered to be of childbearing potential.)
– If yes, has a negative pre-LETAIRIS pregnancy test been confirmed? ☐ Yes ☐ No

Statement of Medical Necessity (This is for insurance purposes only, not to suggest approved uses or indications.)

Diagnosis: Pulmonary Arterial Hypertension (Please select one category below)

☐ Familial (ICD 416.0) ☐ Idiopathic (ICD 416.0) ☐ Scleroderma (ICD 710.1) ☐ HIV (ICD 042 _____) ☐ Lupus (ICD 710.0)

☐ Portal Hypertension (ICD 572.3) ☐ Congenital Heart Defects (ICD 745. _____) ☐ Other: _____ (ICD _____)

By signing, I certify that the above therapy is medically necessary. I have reviewed the Medication Guide and Patient Enrollment Guide with the patient and have counseled the patient on the risks of LETAIRIS, including teratogenicity, decreases in hemoglobin concentration and hematocrit, and the potential risk of reduced male fertility. I will order and review pregnancy tests (for women of childbearing potential) prior to initiation of LETAIRIS treatment, and monthly during treatment in accordance with the LETAIRIS full prescribing information.

REQUIRED
Prescriber Signature: _____ Date: _____

Fax this enrollment form and all patient insurance information, including drug benefit cards (front and back) to 1 888 882 4035.

LETAIRIS Education and Access Program (LEAP)
Instructions

The LETAIRIS Education and Access Program (LEAP) is a restricted program to help prescribers and patients learn about the risks of Letairis® (ambrisentan). To minimize the risk of fetal exposure and adverse fetal outcomes in women of childbearing potential, LETAIRIS is available only through LEAP.

Please complete the following steps prior to faxing the patient enrollment form.

Step 1:	**Check the box** that indicates the patient's preferred Certified Specialty Pharmacy.
Step 2:	**Complete** Patient Information section, including the best method for LEAP to contact your patient.
Step 3:	**Obtain first patient signature.** This is to confirm that the patient has read the LETAIRIS patient Medication Guide and has been informed of the risks of LETAIRIS.
Step 4:	**Obtain second patient signature**. Two signatures are required from the patient. The second is for HIPAA release.
Step 5:	**Complete** Prescriber Information section, including office contact for additional questions regarding this application.
Step 6:	**Complete** Prescription section.
Step 7:	**Provide your signature** on the Prescriber Signature line.

Fax completed form and copies of all relevant insurance information (medical and prescription drug benefits) to **LEAP** at **1-888-882-4035**.

Please visit **www.letairisrems.com** or call **1-866-664-LEAP (5327)** for more information about the LETAIRIS REMS program.

Please see the accompanying patient Medication Guide and full prescribing information, including **boxed WARNING**.

This form is part of an FDA approved REMS.

GILEAD

LETAIRIS Education and Access Program (LEAP) Patient Re-enrollment Form

The LETAIRIS Education and Access Program is a program to help prescribers and patients learn about the risks of Letairis® (ambrisentan). To minimize the risk of fetal exposure and adverse fetal outcomes in women of childbearing potential, LETAIRIS is available only through a restricted program called LEAP.

Patient Information (PLEASE PRINT)

Patient LEAP ID: _____

First Name: _____ Middle Initial: ____ Last Name: _____

Address: _____ City: _____ State: _____ ZIP: _____

Birthdate: ____ /____ /____ Gender: ☐ M ☐ F Phone: (____) _____

Change in Patient Status for Women of Childbearing Potential

If the patient is a woman and has had a change in her childbearing potential, please complete the following section.

☐ **Change in Childbearing Status**

- ☐ Patient is a woman of childbearing potential
- ☐ Patient is a woman NOT of childbearing potential

Prescriber Information (PLEASE PRINT)

Office Contact and E-mail Address: _____

First Name: _____ Last Name: _____ State License No.: _____

Address: _____ City: _____ State: _____ ZIP: _____

Phone: (____) _____ Fax: (____) _____ NPI No.: _____ DEA No.: _____

By signing, I certify that the above therapy is medically necessary. I have reviewed the Medication Guide and Patient Enrollment Guide with the patient and have counseled the patient on the risks of LETAIRIS, including teratogenicity, decreases in hemoglobin concentration and hematocrit, and the potential risk of reduced male fertility. I will order and review pregnancy tests (for women of childbearing potential) prior to initiation of LETAIRIS treatment, and monthly during treatment in accordance with the LETAIRIS full prescribing information.

REQUIRED
Prescriber Signature: _____ Date: _____

Fax: 1-888-882-4035

Please visit **www.letairisrems.com** or call **1-866-664-LEAP (5327)** for more information about the LETAIRIS REMS program.

This form is part of an FDA approved REMS.

GILEAD

Letairis® ambrisentan 5 mg and 10 mg Tablets

Reference ID: 3088104

Letairis®
ambrisentan
5 mg and 10 mg Tablets

FULL PRESCRIBING INFORMATION

The Risk Evaluation and Mitigation Strategy (REMS) Program for LETAIRIS

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

For LETAIRIS, the goals of the REMS program are to:

- Encourage informed benefit-risk decisions regarding the use of LETAIRIS
- Minimize the risk of fetal exposure and adverse fetal outcomes in women of childbearing potential who are prescribed LETAIRIS

In order to ensure that LETAIRIS is prescribed and taken safely, Gilead has worked with the FDA to develop materials for the REMS program to inform prescribers and patients about the risk of serious birth defects.

The LETAIRIS Education and Access Program (LEAP)

Because of the risk of birth defects, LETAIRIS is available only through a restricted program called the LETAIRIS Education and Access Program (LEAP). LEAP works by:

- Providing information to prescribers on the risks of LETAIRIS
- Providing comprehensive education to patients and assistance with obtaining LETAIRIS
- Enrolling both prescribers and patients into the LEAP program
- Controlling dispensing through Certified Specialty Pharmacies

To learn more about the risk of serious birth defects, read the **boxed WARNING** provided below and discuss the Medication Guide with your patients.

LEAP Prescriber Materials

Prescriber Enrollment Materials
Full Prescribing Information
Patient Enrollment/LabSync Order Forms
Patient Re-enrollment Form

LEAP Patient Education Materials

Patient Enrollment Guide
Patient Medication Guide

Overview of LEAP Roles and Responsibilities

The Prescriber:

- Reads the LETAIRIS full prescribing information and understands the risks of LETAIRIS
- Completes a Prescriber Enrollment and Agreement Form and faxes it to LEAP
- Advises the patient that LETAIRIS is only available through a restricted distribution program called LEAP
- Educates the patient about the risks of LETAIRIS using the LETAIRIS Medication Guide and LETAIRIS Patient Enrollment Guide before initiating LETAIRIS treatments, and provides the patient with copies
- Educates and counsels women of childbearing potential on the need to use highly reliable contraception during treatment and for 1 month after stopping treatment, and on the use of emergency contraception in the event of unprotected sex or known or suspected contraception failure
- Orders and reviews pregnancy tests (for women of childbearing potential) prior to initiating treatment and monthly during treatment
- Orders and reviews hemoglobin concentrations and hematocrit prior to initiating treatment with LETAIRIS, at 1 month, and periodically thereafter
- Completes a Patient Enrollment and Consent Form completely and legibly:
  - Confirm patient has agreed to comply with program requirements and has signed the form where indicated
  - As the prescriber, sign the completed form. Fax the completed form, along with all patient insurance information, including prescription drug benefits and medical benefits, to **1-888-882-4035**
  - Keep the original form with the patient's records
- Re-enrolls patients annually. You will be reminded when re-enrollment is required
- Counsels patients who fail to comply with the program requirements and notifies LEAP of any adverse events, including death, or if any patient becomes pregnant during LETAIRIS treatment

LEAP Coordinating Center:

- Enters every LETAIRIS prescriber and patient in the LEAP database
- Works with the Certified Specialty Pharmacy to confirm insurance coverage or investigates alternative sources of reimbursement or assistance
- Sends patient information to the chosen Certified Specialty Pharmacy

The Certified Specialty Pharmacy:

- Files the insurance claim
- Contacts all women of childbearing potential receiving LETAIRIS each month to confirm completion of pregnancy testing and counsel on the risk of teratogenicity
- Contacts all patients to make sure they will be available to receive their LETAIRIS shipment
- Provides a copy of the Medication Guide to patients or caregivers each time LETAIRIS is dispensed and instructs patients to read it each time they receive LETAIRIS
- Answers questions and provides information about LETAIRIS
- Ships LETAIRIS to the patient

The following is a list of participating Certified Specialty Pharmacies:

Accredo
Aetna Specialty Pharmacy
CIGNA Tel-Drug
CuraScript
CVS Caremark
Kaiser Specialty Pharmacy
Walgreens Specialty Pharmacy
WellCare Specialty Pharmacy

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. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%).

Clinical worsening was defined as the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal due to the addition of other PAH therapeutic agents, or study withdrawal due to early escape.[1]

Early escape criteria were two or more of the following after a minimum treatment period of 4 weeks: 20% decrease in 6MWD; worsening WHO functional class; worsening right ventricular failure; rapidly progressing cardiac, hepatic, or renal failure; and refractory systolic hypotension <85 mm Hg.[1,2]

Important Safety Information

BOXED WARNING: CONTRAINDICATED IN PREGNANCY

See *full prescribing information for complete* ***boxed WARNING***.

Do not administer LETAIRIS to a pregnant woman because it may cause fetal harm. LETAIRIS is very likely to produce serious birth defects if used by a pregnant woman. Because of this risk:

- **Exclude pregnancy before the start of treatment and monthly thereafter**
- **Prevent pregnancy during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS, in which case no additional contraception is needed**
- **Educate and counsel women of childbearing potential on the use of emergency contraception in the event of unprotected sex or known or suspected contraceptive failure**
- **LETAIRIS is available only through a restricted program called the LETAIRIS Education and Access Program (LEAP). Prescribers, patients, and pharmacies must enroll in the program. Further information is available at www.letairisrems.com or 1-866-664-LEAP (5327)**

Contraindication

- Do not administer LETAIRIS to a pregnant woman because it can cause fetal harm

Warnings and precautions

- Mild to moderate peripheral edema. Peripheral edema occurred more frequently in elderly patients (age ≥65 years) receiving LETAIRIS (29%; 16/56) compared to placebo (4%; 1/28). Peripheral edema is a known class effect of endothelin receptor antagonists. In addition, there have been postmarketing reports of fluid retention occurring within weeks after starting LETAIRIS that required intervention with a diuretic, fluid management, or, in some cases, hospitalization for decompensating heart failure
- If patients develop acute pulmonary edema during initiation of therapy with vasodilating agents such as LETAIRIS, underlying pulmonary veno-occlusive disease should be considered, and if confirmed, LETAIRIS should be discontinued
- Decreases in sperm count have been observed in patients taking endothelin receptor antagonists
- Decreases in hemoglobin have been observed within the first few weeks of treatment with LETAIRIS, and may persist during treatment. There have been postmarketing reports of anemia requiring transfusion. Measure hemoglobin prior to initiation, at 1 month, and periodically thereafter. Initiation of LETAIRIS therapy is not recommended for patients with clinically significant anemia

Adverse reactions

Adverse Reactions With Placebo-Adjusted Rates >3%

	Placebo (n=132)	LETAIRIS (n=261)	
Adverse reaction	n (%)	n (%)	Placebo-adjusted, %
Peripheral edema	14 (11)	45 (17)	6
Nasal congestion	2 (2)	15 (6)	4
Sinusitis	0 (0)	8 (3)	3
Flushing	1 (1)	10 (4)	3

- During 12-week controlled clinical trials, the incidence of liver aminotransferase (AST, ALT) elevations >3x ULN was 0% for LETAIRIS and 2.3% for placebo
- In postmarketing experience, elevations of aminotransferases have been reported with LETAIRIS use; in most cases alternative causes of the liver injury could be identified (heart failure, hepatic congestion, hepatitis, alcohol use, hepatotoxic medications). In practice, cases of hepatic injury should be carefully evaluated for cause
- Other ERAs have been associated with aminotransferase elevation, hepatotoxicity, and cases of liver failure
- Discontinue LETAIRIS if aminotransferase elevations are >5x ULN or if elevations are accompanied by bilirubin >2x ULN or by signs or symptoms of liver dysfunction, and other causes are excluded

Drug interactions

- Multiple-dose coadministration of LETAIRIS and cyclosporine resulted in an approximately 2-fold increase in LETAIRIS exposure in healthy volunteers. Limit the dose of LETAIRIS to 5 mg once daily when coadministered with cyclosporine

Dosage and administration

- Providers and patients must enroll in the restricted program called LEAP and comply with the required monitoring to ensure safe use
- Initiate treatment at 5 mg once daily, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated
- Tablets may be taken with or without food and should not be split, crushed, or chewed
- Initiate treatment in women of childbearing potential only after a negative pregnancy test and obtain monthly pregnancy tests thereafter
- Not recommended in patients with moderate or severe hepatic impairment. There is no information on the use of LETAIRIS in patients with mild hepatic impairment; however, exposure to LETAIRIS may be increased in these patients

Please see full prescribing information for complete details.

References: 1. LETAIRIS [Prescribing Information]. Foster City, Calif: Gilead Sciences, Inc; February, 2012. **2.** Galiè N, Olschewski H, Oudiz RJ, et al, for the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies (ARIES) Group. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy (ARIES) Study 1 and 2. *Circulation*. 2008;117(23):3010-3019.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
02/15/2012