DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-081

Gilead Sciences, Inc.
Attention: Ms. Linnea Tanner
Director, Regulatory Affairs
Gilead Colorado
7575 West 103rd Ave., Suite #102
Westminster, CO 80021-5426

Dear Ms. Tanner:

Please refer to your new drug application (NDA) dated December 13, 2006 submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Letairis (ambrisentan) 5 and 10 mg Tablets.

We acknowledge receipt of your submission(s) dated January 11 and 26, February 28, March 2, 13, 16, and 26, April 6, 17, and 24, May 1, 11, 14, 15, and 30, and June 1, 6, and 11, 2007.

This new drug application provides for the use of Letairis (ambrisentan) 5 and 10 mg Tablets for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening.

We have completed our review of this application. It is approved with restrictions to assure safe use under the provisions of the Subpart H regulations (21 CFR 314.520), effective on the date of this letter, for use as recommended in the enclosed labeling text, Medication Guide, RiskMAP, and carton and container labels. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced restricted distribution approval regulations.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, Medication Guide, RiskMAP, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 22-081**." Approval of this submission by FDA is not required before the labeling is used.

The Pediatric Research Equity Act is not applicable to drugs granted orphan drug designation.

The postmarketing study commitments that have been agreed upon based on your written correspondence dated 6/15/07 are listed below:

1. Gilead agrees to conduct a study examining the effects of LETAIRIS on 6-minute walk distance at peak and trough plasma concentrations, and further agrees to reach agreement on an appropriate study design with the Division.

   Protocol Submission: by 10/1/2007
   Study Start: by 06/2008
   Final Report Submission: by 12/2009

2. Gilead agrees to submit the results of the Phase 1 ketoconazole drug interaction study that has already been completed.

   Final Report Submission: by 10/2007

3. Gilead agrees to a post-approval commitment to explore the interaction potential of strong inhibitors of CYP2C19 (e.g. omeprazole) on ambrisentan pharmacokinetics in humans. Gilead further agrees to explore the interaction potential of cyclosporine A (strong inhibitor of OATP and P-gp) and rifampin (inhibitor of OATP and inducer of P-gp, CYPs 3A and 2C19) on ambrisentan pharmacokinetics in humans.

   Protocol Submission: by 10/1/2007
   Study Start: by 04/2008
   Final Report Submission: by 12/2008

   This commitment might also be addressed by analysis of existing data.

4. With regard to the RiskMAP, Gilead agrees to submit to the FDA by July 15, 2007, the following documents:
   i. The pregnancy exposure root cause analysis plan including the questionnaire that will be used in the analysis plan;
   ii. The patient and prescriber knowledge, attitude, and behavior survey tools for the RiskMAP evaluation plan;
   iii. The Pharmacy Standard Operating Procedures (SOPs); and
   iv. The Pharmacy Audit Plan.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

As required by 21 CFR 314.550, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of all promotional materials directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

We have determined that Letairis poses a serious and significant public health concern relating to women of child-bearing potential and patients with liver impairment. This concern requires development and distribution of a Medication Guide under 21 CFR 208 in order to prevent serious adverse effects, inform patients of

information concerning risks that could affect their decision to use or continue to use the drug, and/or assure effective use of the drug.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for every patient who is dispensed Letairis. Therefore, format the proposed Medication Guide in a manner that will assure its appropriate distribution to patients and include a plan to ensure distribution. In addition, submit proposed container and/or carton labels for Letairis that include a prominent and conspicuous instruction to provide the Medication Guide to each patient dispensed the drug. The labels must state how the Medication Guide is provided (e.g., affixed on the container, provided with the product, etc.).

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, please call Dan Brum, PharmD, MBA, Regulatory Project Manager, at (301)796-0578.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

GILEAD SCIENCES, INC.

RISK MANAGEMENT PLAN
LETAIRIS™ (AMBRISENTAN)

TABLE OF CONTENTS

6.0 RISK MINIMIZATION ACTION PLAN

The proposed LETAIRIS RiskMAP focuses on reducing the risks of teratogenicity associated with LETAIRIS treatment by using targeted education and outreach to prescribers and patients and a performance-linked, closed distribution system for dispensing LETAIRIS.

While the key goal of the RiskMAP is to minimize the risks of hepatotoxicity and teratogenicity, other risks and safety concerns, including the risk of decreases in hemoglobin concentration and hematocrit and the potential risk of reduced male fertility, will also be addressed in educational materials and tools for prescribers and patients.

Specific elements of the LETAIRIS RiskMAP include:

- Education of prescribers and patients on the risks of hepatotoxicity and teratogenicity associated with LETAIRIS treatment
- Mandatory enrollment of all prescribers into the RiskMAP program, with written self-attestation (Appendix 2)
- Mandatory enrollment of all patients into the RiskMAP program with consent to release health information, and for female patients of childbearing potential, to be contacted if she becomes pregnant to obtain information about the pregnancy (Appendix 3)
- Mandatory liver function testing and pregnancy testing (for female patients of childbearing potential) prior to initiation of LETAIRIS treatment and monthly during treatment
- Mandatory monthly calls to all patients to obtain confirmation that the required testing was completed
- Mandatory monthly calls to all patients to provide counseling on the RiskMAP program requirements and risks of LETAIRIS treatment
- Distribution of LETAIRIS through a performance-linked, closed distribution system that provides LETAIRIS only to patients enrolled in the RiskMAP program. LETAIRIS will be available only through select Specialty Pharmacies
- Packaging of LETAIRIS in a 30-day supply with a Medication Guide
- Re-enrollment of patients into the RiskMAP program after the first 6 months of treatment and annually thereafter

For the purpose of the RiskMAP Program, a female patient of childbearing potential will be defined as a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This definition includes a young woman who has not yet started menstruating.

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 -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.

The LETAIRIS RiskMAP activities will supplement the LETAIRIS labeling and routine pharmacovigilance processes (Section 4.0 of the Risk Management Plan). In addition, there will be an ongoing evaluation of the RiskMAP to provide a continuing and iterative assessment of the effectiveness of the program and of the benefit-risk profile of LETAIRIS.

6.1 RiskMAP Goals

The risk minimization goals of the LETAIRIS RiskMAP are:

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

6.2 RiskMAP Objectives

6.2.1 Objectives for Prescribers

Physicians who prescribe LETAIRIS must be enrolled in the RiskMAP program and understand the risks associated with LETAIRIS treatment including the risks of hepatotoxicity, teratogenicity, decreases in hemoglobin concentration and hematocrit and the potential risk of reduced male fertility. Prior to treating any patient with LETAIRIS, prescribers must:

- Review the RiskMAP educational materials (Appendices 1 through 3)
- Enroll as a prescriber and complete a self-attestation form (Appendix 2) indicating agreement to:
  - Read the full prescribing information (PI) and Medication Guide, for LETAIRIS
  - Enroll all patients in the RiskMAP program

- Review the LETAIRIS Medication Guide and patient education brochure(s) with every patient
- Educate patients on the risks of LETAIRIS, including the risks of hepatotoxicity, teratogenicity, decreases in hemoglobin and hematocrit and the potential risk of reduced male fertility
- Educate female patients of childbearing potential about the need to use two different forms of contraception, including at least one primary form of contraception, simultaneously during LETAIRIS treatment and for one month following treatment discontinuation. If the patient has had a tubal sterilization or a Copper T 380A IUD or LNg 20 IUD inserted, no additional contraception is needed.
  - Primary forms of contraception include tubal sterilization, hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring), IUD and a partner's vasectomy. A Copper T 380A IUD or LNg 20 IUD can be used alone, (i.e. without a secondary form of contraception, as can tubal sterilization).
  - Secondary forms of contraception include barrier contraceptives such as latex condoms, diaphragms and cervical caps
- 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
- 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
- Report any adverse events, including liver injury, and any patient who becomes pregnant during LETAIRIS treatment to Gilead
- Re-enroll patients into the RiskMAP program after the first 6 months of treatment then annually thereafter

Information on enrolled prescribers will be collected in a validated database that captures enrollment data and date of self-attestation; prescribers will be linked to their enrolled patients.

6.2.2 Objectives for Patients

All patients must be enrolled in the RiskMAP program to receive LETAIRIS. In addition, each patient must sign the enrollment form (Appendix 3) indicating they have read the LETAIRIS Medication Guide (Appendix 1) and patient educational materials (Appendix 3) and agree to be contacted, prior to each shipment of LETAIRIS, to obtain confirmation that liver function testing was completed and to be counseled on the requirements of the RiskMAP program and the risks of LETAIRIS.

In addition, each female patient of childbearing potential must:

- Have a pregnancy test before starting LETAIRIS treatment and monthly during LETAIRIS treatment to confirm she is not pregnant
- Agree to be contacted each month to confirm that she completed her pregnancy test

- Use two different forms of contraception, including at least one primary form of contraception, simultaneously during LETAIRIS treatment and for one month following treatment discontinuation. If she has had a tubal sterilization or a Copper T 380A IUD or LNg 20 IUD inserted, no additional contraception is needed.
- Discuss with their prescriber or a healthcare professional with expertise in contraception counseling suitable forms of contraception
- Contact her doctor if she misses a menstrual period or thinks she might be pregnant
- Acknowledge that she will be contacted by the Gilead DSPH Department if she becomes pregnant while on LETAIRIS or within 30 days after treatment discontinuation

Information on enrolled patients will be collected in a validated database that captures enrollment data and self-attestation. The database will link the patient to his/her enrolled prescriber. To protect patient privacy, all patients entered in the database will be assigned a unique identifying number.

6.2.3 Objectives for the RiskMAP Coordinating Center

Gilead will contract an appropriately experienced service organization staffed by technical and healthcare experts to serve as the RiskMAP Coordinating Center for the LETAIRIS RiskMAP.

Specifically, the RiskMAP Coordinating Center must:

- Provide educational materials and tools to enrolled prescribers
- Provide a toll free number that will be appropriately staffed by technical and healthcare professionals to receive calls from prescribers and patients
- Receive and database the prescriber and patient enrollment forms
- Call patients every month to obtain confirmation that liver function testing and pregnancy testing was completed

  For patients who respond affirmatively that they completed the required testing, provide an authorization number to the Specialty Pharmacy allowing the Specialty Pharmacy to dispense a 30-day supply of LETAIRIS

  For patients who are unable to respond affirmatively that they completed the required testing or who cannot be reached:

  - Remind the patient, if possible, of the importance of completing the required testing and instruct the patient to call his/her prescriber to schedule the test(s)
  - Call the patient's prescriber to remind the prescriber of his/her obligation to order and review monthly liver function tests and pregnancy tests (for female patients of childbearing potential)
  - Ask the prescriber whether or not he/she authorizes the refill of LETAIRIS

  - If authorized by the prescriber, provide an authorization number to the Specialty Pharmacy allowing the Specialty Pharmacy to dispense a 30-day supply of LETAIRIS

- Notify Gilead DSPH of any reports of adverse events, including liver injury, and any reports of pregnancy
- Call patients who discontinue LETAIRIS treatment, or their prescriber, to determine the reason for treatment discontinuation
- Reconcile product distribution data received weekly from the Specialty Pharmacy against the list of enrolled patients in the validated RiskMAP database
- Reconcile reports of pregnancies with the DSPH safety database on a regular basis
- Assist in the conduct of prescriber and patient surveys to evaluate prescriber and patient knowledge, attitudes and behaviors regarding LETAIRIS treatment and the RiskMAP program

6.2.4 Objectives for Specialty Pharmacy

LETAIRIS will be available only through select Specialty Pharmacies; therefore, distribution will be closely monitored by Gilead. Specialty Pharmacies will be directed to only ship drug to patients who are enrolled in the RiskMAP program. This agreement will be documented in the contract between the Specialty Pharmacies and Gilead.

Specifically, the Specialty Pharmacies must:

- Only ship drug to patients enrolled in the RiskMAP program and only after the authorization to ship drug has been received from the RiskMAP Coordinating Center
- Counsel patients on the risks of LETAIRIS, including the risks of liver injury and serious birth defects
- Counsel patients on the need to complete a monthly liver function test and pregnancy test (for female patients of child bearing potential)
- Counsel all female patients of childbearing potential on the need to use two different forms of contraception, including at least one primary form of contraception, simultaneously during LETAIRIS treatment and for one month after treatment discontinuation (note that if the patient has had a tubal sterilization or a Copper T 380A IUD or LNg 20 IUD inserted, no additional contraception is needed), and the need to inform their prescriber if they suspect they may be pregnant
- Notify Gilead DSPH of any reports of adverse events, including liver injury, and any reports of pregnancy
- Confirm the drug shipment address with the patient
- Call patients, who discontinue LETAIRIS treatment, or their prescriber, to determine the reason for treatment discontinuation
- Provide weekly product distribution data to the RiskMAP Coordinating Center

The controlled distribution system will allow Gilead to track LETAIRIS shipments and review the location and amount of medication shipped to enrolled prescribers and patients.

The Specialty Pharmacies will be audited at the initiation of the RiskMAP program to ensure procedures are in place to support the RiskMAP requirements. Thereafter, Specialty Pharmacies will be included in the company's annual audit planning.

If Gilead determines that the Specialty Pharmacy is not complying with the RiskMAP program, i.e., is shipping LETAIRIS to patients who are not enrolled in the RiskMAP program, the Specialty Pharmacy may forfeit its authorization to dispense LETAIRIS.

6.3 RiskMAP Strategies and Tools

The tools to be used for the LETAIRIS RiskMAP are shown in Table 6. Qualitative testing, including patient comprehension testing and validation, was performed on patient program materials to ensure the key risk messages were clear and could be followed. The prescriber and patient educational brochures, including the PI and Medication Guide, and the results of the qualitative testing are included as Appendices 1 through 4.

Table 6 RiskMAP Tools by Stakeholder

Stakeholder	Tool	Description
Prescriber	Prescribing Information	Will include information on: • Risk of teratogenicity including: – Pregnancy category "X"; contraindication – Required pregnancy testing prior to and monthly during LETAIRIS treatment • Requirement for female patients of childbearing potential to use two different forms of contraception simultaneously • Warning regarding risk of hepatoxicity and information on required liver function testing prior to and monthly during LETAIRIS treatment • Warning regarding risk of decreased hemoglobin concentraton and hematocrit • Discussion of potential risk of reduced male fertility
	Prescriber Educational Brochure(s)	Describes the risks of LETAIRIS™ and the RiskMAP goals and requirements, including: • Prescriber and patient enrollment • Prescriber and patient education • Pregnancy testing requirements
	Enrollment and Self-attestation Form	Enrolls prescriber into RiskMAP program. Includes self-attestation checklist of all prescriber obligations including: • Patient education and counseling • Patient enrollment • Pregnancy and liver function testing requirements

Stakeholder	Tool	Description
Prescriber, cont.	Sales Force Training Materials	Presentation used by Sales Force to educate prescribers on the RiskMAP program
	Medical Science Liaison (MSL) Training Materials	Presentation used by MSLs to educate prescribers on the RiskMAP program
	Link to RiskMAP program details on Gilead website (www.gilead.com) and product website (www.letairis.com)	Provides program information, including risks of LETAIRIS and RiskMAP program requirements, and all prescriber and patient educational materials and enrollment forms
	RiskMAP Coordinating Center Toll-free help line	Provides health care professionals with medical information concerning LETAIRIS and the RiskMAP program
Patient	Medication Guide	Summarizes important information in language that is easy to read and understand following the FDA specified format. A Medication Guide will be provided with every prescription of LETAIRIS
	Enrollment and Agreement Form	Includes consent to provide health information and acknowledgement by patients that they will be contacted monthly as part of the RiskMAP program and attestation that they reviewed the Medication Guide and patient educational brochure(s) Requires prescriber signature acknowledging he/she educated the patient on the risks of LETAIRIS and the requirements of the RiskMAP program and reviewed with the patient the Medication Guide and educational brochure(s).
	Patient Educational Brochure(s)	Describes the risks of treatment with LETAIRIS and the requirements of the RiskMAP program, including the need for liver function testing and pregnancy testing prior to and monthly during LETAIRIS treatment.
	Link to RiskMAP details on Gilead website (www.gilead.com) and product website (www.letairis.com)	Provides program information, including risks of LETAIRIS and requirments of the RiskMAP program and all prescriber and patient educational materials and enrollment forms
	RiskMAP Coordinating Center Toll-free help line	Provides patients with medical information concerning LETAIRIS and the RiskMAP program
RiskMAP Coordinating Center	Contract	The RiskMAP Coordinating Center will have a contract with Gilead that clearly dileneates the service provider's responsibilities.
Specialty Pharmacy	Contract	Each Specialty Pharmacy will have a contract with Gilead in which they agree to dispense LETAIRIS only to prescribers and patients who are enrolled in the RiskMAP program
	Inventory Tracking Log	Documentation of dispensing to prescribers and patients enrolled in the RiskMAP program

6.3.1 Strategies and Tools for Prescribers

Prescribers will be informed of the RiskMAP program through instructional materials including the PI, prescriber educational brochure(s), patient educational brochure(s), visits from Gilead's sales force and/or Medical Science Liaisons (MSL), educational programs at professional meetings, and information on the Gilead website (www.gilead.com) and the product website (www.letairis.com).

LETAIRIS prescribers who have been educated about the risks associated with LETAIRIS must enroll in the RiskMAP program in order to prescribe LETAIRIS. Enrollment includes a one-time attestation that the prescriber understands the risks of LETAIRIS and will counsel all patients about these risks of LETAIRIS, will review with each patient the Medication Guide and patient educational brochure(s) and will order and review liver function tests and pregnancy tests (for female patients of childbearing potential) prior to initiation of LETAIRIS treatment and monthly during LETAIRIS treatment.

The prescriber also agrees to educate female patients of child bearing potential on the need to use two different forms of contraception, including at least one primary form of contraception, simultaneously during LETAIRIS treatment and for one month following treatment discontinuation, unless the patient has had a tubal sterilization or a Copper T 380A IUD or LNg 20 IUD inserted, in which case no additional contraception is needed.

The prescriber educational brochure and enrollment form (Attachment 2) provide the RiskMAP program definition for female patients of childbearing potential as well as information on primary and secondary forms of contraception.

Enrollment forms will be provided by the Gilead sales force and MSLs, or by download from the Gilead website. Prescribers can also call the RiskMAP Coordinating Center using a toll-free telephone number to request an enrollment form or receive information about LETAIRIS and the RiskMAP program.

Prescribers will be required to re-enroll patients into the RiskMAP program after the first 6 months of treatment then annually thereafter. If the patient changes physicians, a new enrollment form will be required. The patient information from the new prescriber will be linked in the RiskMAP program database with information from the prior prescriber. This re-enrollment will serve to reinforce the risks and benefits of LETAIRIS. Prescribers will also be informed of the need to report any adverse events, including liver injury, and any pregnancy that occurs to Gilead.

6.3.2 Strategies and Tools for Patients

To receive LETAIRIS treatment, patients must be enrolled in the RiskMAP program. To enroll a patient in the RiskMAP program, the prescriber will complete a patient enrollment form (Appendix 3) that collects basic patient identifying and contact information as well as insurance coverage data needed to obtain reimbursement for LETAIRIS. The prescriber will also assess whether the patient is a female patient of child bearing potential and, if the patient is of child bearing potential, confirm that a pregnancy test was completed and that the test was negative.

The patient will sign the enrollment form indicating they have read the Medication Guide and patient educational brochure(s) and agree to be contacted for counseling on the RiskMAP program requirements and risks of LETAIRIS and to obtain confirmation that liver function

testing and pregnancy testing (for female patients of childbearing potential) was completed. Female patients of childbearing potential also agree that, if they become pregnant, they will be contacted by the Gilead DSPH Department. The prescriber will also sign the form indicating they have educated the patient on the requirements of the RiskMAP program and the risks of treatment with LETAIRIS and have reviewed the Medication Guide and patient educational brochure(s) with the patient. The form will then be faxed to the RiskMAP Coordinating Center.

Upon receiving the enrollment form, The RiskMAP Coordinating Center will verify that the prescriber indicated (by checking or ticking the appropriate boxes on the patient enrollment form) that the required testing was completed and enter the patient into the database. The RiskMAP Coordinating Center will then authorize the Specialty Pharmacy to ship LETAIRIS. The Specialty Pharmacy will ship LETAIRIS to the patient, as directed.

Patient educational brochures that discuss the appropriate use of LETAIRIS, the risks associated with LETAIRIS treatment and the requirements for receiving LETAIRIS treatment will be sent with the first shipment of LETAIRIS. A Medication Guide will be provided with each 30-day supply of LETAIRIS.

Patients will be called every month by the RiskMAP Coordinating Center to obtain confirmation that liver function testing and pregnancy testing (for female patients of child bearing potential) was completed. If the patient responds affirmatively that he/she has completed the required test(s), the RiskMAP Coordinating Center will provide authorization for the Specialty Pharmacy to dispense a 30-day supply of LETAIRIS.

If the patient is unable to respond affirmatively to completing the required testing, or if the RiskMAP Coordinating Center is unable to reach the patient, the RiskMAP Coordinating Center will contact the patient's prescriber.

All patients will be called by the Specialty Pharmacy, prior to dispensing each 30-day supply of LETAIRIS, to receive counseling on the risks and requirements of LETAIRIS treatment including, the need to have a monthly test to check their liver function and, for female patients of childbearing potential, the need to complete a monthly pregnancy test, to use two different forms of contraception, and to inform their prescriber immediately if they suspect they may be pregnant.

Finally, all patients who discontinue treatment will be called to determine the reason for treatment discontinuation.

6.3.3 Strategies and Tools for the RiskMAP Coordinating Center

Gilead will contract a qualified service provider to serve as the RiskMAP Coordinating Center. By contract, the RiskMAP Coordinating Center will agree to:

- Train all RiskMAP staff on the RiskMAP program procedures and all RiskMAP materials prior to initiation of the RiskMAP Program
- Provide a toll free number that will be appropriately staffed by technical and healthcare professionals to receive calls from prescribers and patients
- Receive and database the prescriber and patient enrollment forms

- Call patients every month to obtain confirmation that liver function testing and pregnancy testing (for female patients of childbearing potential) were completed
- Notify Gilead DSPH of any reports of adverse events, including liver injury, or any report of pregnancy
- Call patients, who discontinue LETAIRIS treatment, or their prescriber, to determine the reason for treatment discontinuation
- Reconcile product distribution data received weekly from the Specialty Pharmacy against the list of enrolled patients in the validated RiskMAP database
- Reconcile reports of pregnancies with the DSPH safety database on a regular basis
- Allow audits by the FDA, Gilead, or a third party designated by Gilead

6.3.4 Strategies and Tools for Specialty Pharmacy

Gilead will contract select Specialty Pharmacies to distribute LETAIRIS directly to enrolled patients or prescribers. One element of the contract is an agreement to ship LETAIRIS only to enrolled patients.

Specialty Pharmacies will receive authorization to dispense LETAIRIS from the RiskMAP Coordinating Center. LETAIRIS will be packaged in a 30-day supply and will require monthly refills.

Specifically, the designated representative of each Specialty Pharmacy agrees that:

- Training of pharmacy staff on the RiskMAP program procedures and materials has been completed prior to dispensing drug
- LETAIRIS will only be shipped to patients enrolled in the RiskMAP program and only after authorization has been received from the RiskMAP Coordinating Center
- All patients will be counseled on the risks of LETAIRIS treatment, including the risks of liver injury and serious birth defects
- All patients will be counseled on the need to complete monthly liver function testing and pregnancy testing (for female patients of childbearing potential)
- All female patients of childbearing potential will be counseled on the need to use two different forms of contraception, including at least one primary form of contraception, simultaneously during and for one month after treatment discontinuation (unless the patient has had a tubal sterilization or a Copper T 380A IUD or LNg 20 IUD inserted, in which case no additional contraception is needed) and the need to inform their prescriber if they suspect they may be pregnant
- Gilead will be notified of any reports of adverse events, including liver injury, or any report of pregnancy
- Patients who discontinue LETAIRIS treatment, or their prescriber, will be called to determine the reason for treatment discontinuation
- Each patient will receive a Medication Guide with each LETAIRIS shipment
- An inventory tracking log must be completed for every shipment of LETAIRIS

- The Specialty Pharmacy may be audited by the FDA, Gilead, or a third party designated by Gilead
- Noncompliance with the RiskMAP program could result in loss of the ability to dispense LETAIRIS

6.4 Key Risk Messages

The key risk messages of the LETAIRIS RiskMAP will be:

- LETAIRIS may cause liver injury
  - LETAIRIS treatment is not recommended for patients with moderate to severe hepatic impairment
  - All patients must have liver function tests (including aminotransferases and bilirubin) before starting LETAIRIS treatment
  - All patients must have liver function tests (including aminotransferases and bilirubin) each month during LETAIRIS treatment
- LETAIRIS can cause major birth defects if taken during pregnancy
  - A woman must not be pregnant when she starts LETAIRIS
  - A pregnancy test must be done before starting LETAIRIS treatment
  - A woman must not become pregnant while being treated with LETAIRIS
  - Pregnancy tests must be done monthly during LETAIRIS treatment
  - Women of childbearing potential must use two different forms of contraception, including at least one primary form of contraception, simultaneously during LETAIRIS treatment and for one month following treatment discontinuation, unless the patient has had a tubal sterilization or a Copper T 380A IUD or LNg 20 IUD inserted, in which case no additional contraception is needed
  - Prescribers should counsel female patients of childbearing potential on suitable forms of contraception or refer the patient to a healthcare professional with expertise in contraception for such counseling

While the key goal of the RiskMAP is to minimize the risks of liver injury and serious birth defects, other risks, including the risk of decreases in hemoglobin concentration and hematocrit and the potential risk of reduced male fertility, will also be addressed in educational materials and tools for prescribers and patients.

6.5 Compliance

6.5.1 Prescriber Compliance

Prescriptions written by prescribers who are not enrolled in the RiskMAP program will not be filled by the Specialty Pharmacy. The Specialty Pharmacy will notify the RiskMAP Coordinating Center if a prescription is presented from a prescriber who is not enrolled in the RiskMAP program. The RiskMAP Coordinating Center will call the physician and discuss the requirements of the RiskMAP program and provide him/her with the ability to receive educational materials and an enrollment form.

6.5.2 Patient Compliance

Every month the RiskMAP Coordinating Center will call patients to obtain confirmation that liver function testing and pregnancy testing (for female patients of childbearing potential) were completed. If the patient is unable to respond affirmatively that they have completed the required testing, or if the RiskMAP Coordinating Center is unable to reach the patient, the RiskMAP Coordinating Center will contact the patient's prescriber. The RiskMAP Coordinating Center will remind the prescriber of his/her obligation to order and review monthly liver function tests and pregnancy tests (for female patients of childbearing potential).

Patient compliance with liver function and pregnancy testing requirements will be collected and reported on a regular basis.

Any patient who becomes pregnant while treated with LETAIRIS will be followed by the Gilead DSPH Department according to its established internal processes for the term of their pregnancy to assess the outcome of exposure to LETAIRIS. All data collected will be entered into the Gilead DSPH Database (ARISg). Data collected in the database will be used to evaluate the effectiveness of the LETAIRIS RiskMAP by identifying the possible reasons why a patient became pregnant despite the warnings and requirement to complete monthly pregnancy testing prior to receiving LETAIRIS. All pregnancies will be evaluated retrospectively and in aggregate on a regular basis.

Gilead will forward data about all cases of pregnancy received by the DSPH Department to the RiskMAP Coordinating Center for entry into the RiskMAP database. Both databases will be reconciled on a regular basis.

All reports of pregnancy will be reported to the Agency on an expedited basis.

Gilead will also report cases of liver injury to the Agency on an expedited basis. Cases of liver injury that would require expedited reporting will include:

- Cases of liver injury that result in death, hospitalization, liver transplantation or being listed for liver transplantation
- Liver function tests (LFTs) indicating:
  - Serum aminotransferase elevations >8x the upper limit of normal (ULN); or
  - Serum aminotransferase elevations >2xULN accompanied by increases in bilirubin ≥2xULN

6.5.3 RiskMAP Coordinating Center Compliance

The RiskMAP Coordinating Center will be audited at the initiation of the RiskMAP Program to ensure procedures are in place to support the RiskMAP requirements. Thereafter the RiskMAP will be included in the company's annual audit planning.

Audits will include, but are not limited to, the following: 1) review of contract in place between Gilead and the RiskMAP Coordinating Center and compliance with requirements of the contract, 2) review RiskMAP Coordinating Center practice for confirming and linking prescriber and patient enrollment in RiskMAP program, 3) confirming that the RiskMAP Coordinating Center is calling patients to obtain confirmation that the required testing was completed, 4) review of process for providing shipment authorization number to the

Specialty Pharmacy, 5) review process for reconciling product distribution data against list of enrolled patients, and 6) review of compliance with other relevant requirements such as adverse event and product complaint reporting procedures.

6.5.4 Specialty Pharmacy Compliance

If Gilead determines that the Specialty Pharmacy is not complying with the RiskMAP program, i.e., is shipping LETAIRIS to patients who are not enrolled in the RiskMAP program, the Specialty Pharmacy may forfeit its authorization to dispense LETAIRIS.

The Specialty Pharmacies will be audited at the initiation of the RiskMAP Program to ensure procedures are in place to support the RiskMAP requirements.

Thereafter, Specialty Pharmacies will be included in the company's annual audit planning.

Audits will include, but are not limited to, the following: 1) review of contract in place between Gilead and Specialty Pharmacy and compliance with requirements of the contract, 2) review Specialty Pharmacy practice for confirming patient enrollment in RiskMAP program, 3) review of pharmacy dispensing documentation, 4) confirmation of receipt of authorization number by Specialty Pharmacy from RiskMAP Coordinating Center prior to dispensing, 5) confirmation of Specialty Pharmacy counseling patients regarding the risks of LETAIRIS and the requirements of the RiskMAP program, 6) confirmation of any enrollment forms or prescriptions received by the Specialty Pharmacy being routed to the RiskMAP Coordinating Center, and 7) review of compliance with other relevant requirements such as adverse event and product complaint reporting procedures.

6.6 LETAIRIS RiskMAP Evaluation

6.6.1 Core Safety Review Committee

Gilead is committed to evaluating the effectiveness of the RiskMAP program and reporting results to the FDA quarterly for 2 years after program initiation, then on an annual basis thereafter. Each submission will include data from the RiskMAP program including cases of liver injury and reports of pregnancy exposures.

Specifically, the reports will include:

- Reports of operational audits, including results of distribution data reconciliation
- Results of physician and patient surveys
- The total number of patients and female patients of childbearing potential receiving the product
- Drug use patterns (reasons for use, patient demographics, prescribing medical specialties)
- In the case of pregnancy, the root-cause analysis to determine the reason for the pregnancy exposure
- The number of pregnancy exposures (pregnancy exposures will be recorded within the RiskMAP database as well as the global safety database, with appropriate linkage to allow matching of the cases reported in the RiskMAP database to cases in the global safety database)
- The number (percent) patient reported compliance with:

  - Monthly pregnancy testing for female patients of child bearing potential by quarter and overall
  - Contraception requirements by quarter and overall
  - Liver function testing by quarter and overall
- An analysis of the numbers and reasons for pharmacist calls to prescribers
- The frequency of interruptions in therapy, why such interruptions occurred, and how long the shipment was delayed (e.g., the number of times a shipment was held because the patient had not had their monthly laboratory tests)
- The number and reasons for discontinuation therapy with ambrisentan
- The frequency and reasons for dispensing >30 day supply.

The multidisciplinary Core Safety Review Committee including senior representatives from the Gilead DSPH, Regulatory, Legal, and Clinical departments will review the compiled data and evaluate the effectiveness of the RiskMAP. The Committee will identify areas for improvement, if required.

6.6.2 Compliance Review Subcommittee

A cross-functional team will be formed that will serve as a Compliance Review Subcommittee. The function of this committee is to facilitate RiskMAP compliance. The committee will meet on a regular basis, and ad hoc as needed, to review results from the monitoring of operational processes, distribution data, and audit data. The committee will determine appropriate corrective action to address non-compliance by stakeholders and ensure continuous improvement of all RiskMAP activities.

6.6.3 Evaluation Measures

The evaluation measures that will be implemented include surveys of prescribers and patients, auditing of the RiskMAP program processes, and tracking LETAIRIS distribution from the Specialty Pharmacies.

A complete evaluation plan for assessing patient and prescriber knowledge, attitude and behavior and the survey instruments used to collect the information will be submitted to the Agency separately. The anticipated process for administering the surveys follows.

6.6.3.1 Knowledge, Attitude and Behavior Survey of Prescribing Physicians

On a quarterly basis, the RiskMAP Coordinating Center will administer surveys to a random sample of prescribing physicians. The process for administering surveys will be:

- A random sample to enrolled prescribers will be selected (without replacement)
- The first contact will be by US mail. The mailing will contain the survey and a return postage paid envelope for sending the survey to the RiskMAP Coordinating Center. If the prescribing physician has provided an e-mail address, the survey will also be provided by e-mail. The mailing will include a web address where the prescribing physician can complete the survey online.

- If the physician does not provide a response to the survey within 2 weeks, a fax will be sent to the physician containing the same survey
- If no response is obtained from the fax after a 1-week period, then the physician will be contacted by telephone
- Interviewers at the RiskMAP Coordinating Center will make 3 attempts to reach the physician and administer the survey
- All attempts to contact the physician will be documented

The survey will include questions concerning:

- Prescribing physician knowledge about the benefits and risks of LETAIRIS treatment, including hepatotoxicity and teratogenicity
- Prescribing physician behavior regarding patient counseling, laboratory testing, and pregnancy counseling
- Availability and use of the RiskMAP program patient educational tools in the physician office

6.6.3.2 Knowledge, Attitude and Behavior Survey of Patients

On a quarterly basis, the RiskMAP Coordinating Center will administer surveys to a random sample of patients who are being treated with LETAIRIS. The process for administering the surveys will be:

- A random sample of enrolled patients will be selected (without replacement). The sample will be stratified by duration of LETAIRIS use, to include new patients (having their first prescription) and patients who have been treated for at least 3 months
- The first contact will be by US mail. The mailing will contain the survey and a return postage paid envelope for sending the survey to the RiskMAP Coordinating Center. If the patient has provided an e-mail address, the survey will also be provided by e-mail. The mailing will include a web address where the prescribing physician can complete the survey online.
- If the patient does not provide a response to the mail survey within 2 weeks, a second mailing will be sent containing the same survey
- If no response is obtained from the second mailing after a 1-week period, then the patient will be contacted by telephone
- Interviewers at the RiskMAP Coordinating Center will make 3 attempts to reach the patient and administer the survey
- All attempts to contact the patient will be documented

The survey will include questions concerning:

- Patient knowledge about the risks of LETAIRIS treatment, including liver injury and serious birth defects
- Patient behavior regarding pregnancy testing and other required testing

- Patient attitude toward contraception (female patients of childbearing potential only)
- Availability and use of the RiskMAP patient educational tools in the physician office

6.6.4 Recommendation Generation and Implementation

In addition to the individual case evaluation, on an annual basis the Gilead DSPH team will review all information collected during that time period to identify systematic causes for which program changes can be initiated in an effort to reduce the number of pregnancies among women treated with LETAIRIS.

6.6.5 RiskMAP Coordinating Center and Specialty Pharmacy Reconciliation of Inventory and Distribution

The RiskMAP Coordinating Center will receive product distribution data electronically from each Specialty Pharmacy every week. The RiskMAP Coordinating Center will be responsible for reconciling the product distribution data against the list of enrolled patients in the validated RiskMAP database.

These weekly reconciliations will verify that LETAIRIS is shipped only to patients enrolled in the RiskMAP program.

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

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?

- **Possible liver injury.**

  LETAIRIS can cause liver injury. You must have a blood test to check your liver function before you start LETAIRIS and each month after that. Your doctor will order these blood tests. (See "What are the possible side effects of LETAIRIS?" for information about the signs of liver problems.) **Tell your doctor if you have had moderate or severe liver problems, including liver problems while taking other medicines.**

- **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 different reliable forms of birth control at the same time, during LETAIRIS treatment and for one month after stopping LETAIRIS. 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. 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.
- y**our blood tests show possible liver injury.**

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.

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.
- During treatment your doctor will test your blood for signs of side effects to your liver and red blood cells.

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:

- **Possible liver injury.** (See "What is the most important information I should know about LETAIRIS?") Call your doctor right away if you have any of these symptoms of liver problems: loss of appetite, nausea, vomiting, fever, unusual tiredness, right upper stomach pain, yellowing of the skin or the whites of your eyes (jaundice), dark urine, or itching.
- **Serious birth defects.** (See "What is the most important information I should know about LETAIRIS?")
- **Low sperm count.** LETAIRIS can lower sperm count in animals. If this happens in men, they may lose the ability to father children. Talk with your doctor if you have any questions or concerns.

The most common side effects of LETAIRIS are:

- Lowering of red blood cell count
- Swelling of legs and ankles (edema)
- Stuffy nose (nasal congestion)
- Inflamed nasal passages (sinusitis)
- Hot flashes or getting red in the face (flushing)
- Feeling your heart beat (palpitations)
- Red and sore throat and nose
- Stomach pain
- Constipation
- Shortness of breath
- Headache

How should I store LETAIRIS?

Store LETAIRIS at less than 86 °F (30 °C), in the package it comes in.

General information about LETAIRIS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any concerns or questions about LETAIRIS, ask your doctor or other healthcare provider. This Medication Guide is only a summary of some important information about LETAIRIS. Your doctor can give you information about LETAIRIS that was written for healthcare professionals. Do not use LETAIRIS

for any condition other than that for which it was prescribed. Do not share LETAIRIS with other people. It may harm them.

Call 1-866-664-LEAP (5327) or visit www.letairis.com or www.gilead.com for more information.

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.

This medication guide has been approved by the U.S. Food and Drug Administration.

Gilead Sciences, Inc., Foster City, CA 94404

June 2007

GS22-081-000

LEAP Prescribing Physician Enrollment and Agreement Form

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

Prescribing Physician Information

First Name _____ Middle Initial _____ Last Name _____ Suffix _____

Specialty _____ Name of Facility _____ Office Contact _____

Address _____ City _____ State _____ ZIP _____

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

State License # _____ NPI # _____ DEA # _____

Prescribing Physician Agreement

By signing below, you signify your understanding of the risks of LETAIRIS™ (ambrisentan) treatment and your obligation as a LETAIRIS prescribing physician 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 will discuss the risks of LETAIRIS with each patient prior to prescribing LETAIRIS, including the risks of hepatotoxicity, teratogenicity, decreases in hemoglobin concentration and hematocrit, and the potential risk of reduced male fertility.
- I will review the patient Medication Guide and patient education brochure with each patient prior to prescribing LETAIRIS.
- I will order and review liver function tests (including aminotransferases and bilirubin) and pregnancy tests (for female patients of childbearing potential*) prior to initiating treatment with LETAIRIS and monthly during treatment.
- I will educate and counsel female patients of childbearing potential about the need to use 2 different forms of contraception, including at least 1 primary form of contraception, simultaneously during LETAIRIS treatment and for 1 month following treatment discontinuation. If the patient has had a tubal sterilization or a Copper T 380A IUD or LNg 20 IUD inserted, no additional contraception is needed.
  - Primary forms of contraception include tubal sterilization, hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring), IUD, and a partner's vasectomy. A Copper T 380A IUD or LNg 20 IUD can be used alone (i.e., without a secondary form of contraception, as can tubal sterilization).
  - Secondary forms of contraception include barrier contraceptives such as latex condoms, diaphragms, and cervical caps.
- I will counsel patients on suitable forms of contraception or refer the patient to a healthcare professional with experience in contraception for counseling.
- I will measure hemoglobin and hematocrit prior to initiating treatment with LETAIRIS, at 1 month, and periodically thereafter.
- I will counsel patients who fail to comply with the program requirements.
- I will notify LEAP of any adverse events, including liver injury, or if any patient becomes pregnant during LETAIRIS treatment.
- I agree to re-enroll appropriate patients after the first 6 months and annually thereafter by completing and submitting a new patient enrollment form.

Prescribing Physician Signature _____ **Date** _____

If you have any questions, please call 1-866-664-LEAP (5327).

Please visit www.letairis.com or www.gilead.com for more information.

*See reverse side for definition of a female patient of childbearing potential.

*The prescribing physician must determine if a female patient is of childbearing potential before enrolling her in LEAP.

Definition of a Female Patient of Childbearing Potential

A female patient of childbearing potential is a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This definition includes a young woman who has not yet started menstruating.

A woman who has had a tubal sterilization is considered to be of childbearing potential in LEAP.

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.

There is no need to fax this side of the form.

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

WARNING: POTENTIAL LIVER INJURY

LETAIRIS (ambrisentan) can cause elevation of liver aminotransferases (ALT and AST) to at least 3 times the upper limit of normal (ULN). LETAIRIS treatment was associated with aminotransferase elevations >3x ULN in 0.8% of patients in 12-week trials and 2.8% of patients including long-term open-label trials out to one year. One case of aminotransferase elevations >3x ULN has been accompanied by bilirubin elevations >2x ULN. Because these changes are a marker for potentially serious liver injury, serum aminotransferase levels (and bilirubin if aminotransferase levels are elevated) must be measured prior to initiation of treatment and then monthly.

In the post-marketing period with another endothelin receptor antagonist (ERA), bosentan, rare cases of unexplained hepatic cirrhosis were reported after prolonged (>12 months) therapy. In at least one case with bosentan, a late presentation (after >20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of the suspect drug. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment.

Elevations in aminotransferases require close attention. LETAIRIS should generally be avoided in patients with elevated aminotransferases (>3 x ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin >2 x ULN, treatment should be stopped. There is no experience with the re-introduction of LETAIRIS in these circumstances.

CONTRAINDICATION: PREGNANCY

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 (4.1)]*. Pregnancy must therefore be excluded before the initiation of treatment with LETAIRIS and prevented thereafter by the use of at least two reliable methods of contraception unless the patient has had a tubal sterilization or Copper T 380A IUD or LNg 20 IUD inserted, in which case no other contraception is needed. Obtain monthly pregnancy tests.

Because of the risks of liver injury and birth defects, LETAIRIS is available only through a special restricted distribution program called the LETAIRIS Education and Access Program (LEAP), by calling 1-866-664-LEAP (5327). Only prescribers and pharmacies registered with LEAP may prescribe and distribute LETAIRIS. In addition, LETAIRIS may be dispensed only to patients who are enrolled in and meet all conditions of LEAP *[see WARNINGS, Prescribing and Distribution Program for LETAIRIS]*.

If you have questions or would like additional information, please call 1-866-664-LEAP (5327) or visit www.letairis.com or www.gilead.com

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

GILEAD

Letairis™
ambrisentan
5 mg and 10 mg Tablets

LETAIRIS EDUCATION AND ACCESS PROGRAM (LEAP)

Prescriber Information

INDICATION: LETAIRIS is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in patients with WHO Class II or III symptoms to improve exercise capacity and delay clinical worsening.

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

Letairis™
ambrisentan
5 mg and 10 mg Tablets

About LEAP

LEAP is a program to help you and your patients learn about the risks of LETAIRIS™ (ambrisentan), including the serious risks of liver injury and birth defects. Because of the risk of liver injury, and in an effort to make the chance of fetal exposure to LETAIRIS as small as possible, LETAIRIS may be prescribed only through LEAP by calling 1-866-664-LEAP (5327).

LEAP works by:

- Providing information to prescribers on the risks of LETAIRIS
- Providing comprehensive education to patients and assistance with obtaining LETAIRIS
- Requiring enrollment of both prescriber and patient in LEAP
- Controlling dispensing through a specialized distribution network (specialty pharmacies)

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

LEAP Overview

The Prescriber:

- **Completes a one-time Prescriber Enrollment and Agreement Form and faxes it to LEAP**
- **Counsels each patient on the risks of LETAIRIS treatment**
- **Reviews the patient Medication Guide and patient education brochure with the patient**
- **Orders and reviews liver function tests (including aminotransferases and bilirubin) and pregnancy tests prior to initiating treatment with LETAIRIS and monthly during treatment**
- **Orders and reviews hemoglobin concentrations and hematocrit prior to initiating treatment with LETAIRIS, at 1 month, and periodically thereafter**
- **Assists patient with choosing a specialty pharmacy**
- **Completes a Patient Enrollment and Consent Form for each patient and faxes it to LEAP**
- **Re-enrolls appropriate patients after the first 6 months and annually thereafter**

LEAP:

- **Enters every LETAIRIS prescriber and patient in the LEAP database**
- **Confirms insurance coverage or investigates alternative sources of reimbursement or assistance**
- **Sends patient information to the chosen specialty pharmacy**
- **Contacts patients each month to obtain confirmation that they completed the required testing**

The Specialty Pharmacy:

- **Files the insurance claim**
- **Answers questions and provides information about LETAIRIS**
- **Ships LETAIRIS to the patient**

Prescriber Enrollment

Physicians who wish to prescribe LETAIRIS must enroll in LEAP by completing a one-time Prescriber Enrollment and Agreement Form that states they will comply with the program requirements. The Prescriber Enrollment and Agreement Form is in the pocket of the back cover of this brochure.

The prescribing physician agrees to:

- Read the LETAIRIS full prescribing information and understand the risks of LETAIRIS.
- Use the patient Medication Guide and patient education brochure to educate the patient and discuss the risks of LETAIRIS.
- Enroll all patients prescribed LETAIRIS in LEAP and re-enroll appropriate patients after the first 6 months and annually thereafter.
- Discuss with female patients of childbearing potential the need to use 2 different forms of contraception, including at least 1 primary form of contraception, simultaneously during LETAIRIS treatment and for 1 month following treatment discontinuation. If the patient has had a tubal sterilization or a Copper T 380A IUD or LNg 20 IUD inserted, no additional contraception is needed.
  - Primary forms of contraception include tubal sterilization, hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring), IUD, and a partner's vasectomy. A Copper T 380A IUD or LNg 20 IUD can be used alone (i.e., without a secondary form of contraception, as can tubal sterilization).
  - Secondary forms of contraception include barrier contraceptives such as latex condoms, diaphragms, and cervical caps.
- Order and review liver function tests (including aminotransferases and bilirubin) and pregnancy tests prior to initiating treatment with LETAIRIS and monthly during treatment.
- Order and review hemoglobin concentrations and hematocrit prior to initiating treatment with LETAIRIS, at 1 month, and periodically thereafter.
- Counsel patients who fail to comply with the program requirements and notify LEAP of any adverse events, including liver injury, or if any patient becomes pregnant during LETAIRIS treatment.

Prescribers must complete, sign, and fax the Prescriber Enrollment and Agreement Form. **FAX**: 1-888-882-4035.

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

Patient Enrollment

LETAIRIS is available only to patients enrolled in LEAP. To enroll a patient in LEAP, complete the following steps:

1. Fill out the Patient Enrollment and Consent Form completely and legibly.
2. Use the patient Medication Guide and patient education brochure to educate the patient about the risks of LETAIRIS.
3. Counsel females of childbearing potential* on the need to use 2 different forms of contraception, including at least 1 primary form, simultaneously during LETAIRIS treatment and for 1 month following treatment discontinuation.
4. Schedule monthly liver function tests (including aminotransferases and bilirubin) and pregnancy tests.
5. Help the patient choose a specialty pharmacy.
6. Confirm that the patient has agreed to comply with program requirements and has signed the form where indicated.
7. Provide the LEAP Patient Enrollment Guide to the patient.
8. Sign and fax the completed Patient Enrollment and Consent Form. **FAX**: 1-888-882-4035.
9. Keep the original form with the patient's records.
10. Re-enroll appropriate patients after the first 6 months and annually thereafter. You will be reminded when re-enrollment is required.

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

Definition of a Female Patient of Childbearing Potential

A female patient of childbearing potential is a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This definition includes a young woman who has not yet started menstruating.

A woman who has had a tubal sterilization is considered to be of childbearing potential in LEAP.

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.

Please see the following pages for risks of hepatotoxicity, teratogenicity, decreases in hemoglobin concentration and hematocrit, potential risk of reduced male fertility, coadministration with cyclosporine A, and adverse reactions.

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

LETAIRIS Risk Information

Letairis™ ambrisentan
5 mg and 10 mg Tablets

Education is a key component of risk management. Prescribers must review the LETAIRIS full prescribing information to prepare for patient counseling. This brochure 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) in patients with WHO Class II or III symptoms to improve exercise capacity and delay clinical worsening.

Risk of Hepatotoxicity

Treatment with ERAs has been associated with dose-dependent liver injury manifested primarily by elevation of serum aminotransferases (ALT or AST), but sometimes accompanied by abnormal liver function (elevated bilirubin). The combination of aminotransferases greater than 3 times the upper limit of normal (>3× ULN) and total bilirubin ≥2× ULN is a marker for potentially serious hepatic injury. Liver function tests (including aminotransferases and bilirubin) must be measured prior to initiating treatment with LETAIRIS and monthly during treatment.

LETAIRIS is not recommended in patients with moderate or severe hepatic impairment. Use caution in patients with mild hepatic impairment.

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.

Female patients of childbearing potential must agree to the following:

- A negative pregnancy test prior to treatment initiation is required.
- Monthly pregnancy testing during LETAIRIS treatment.
- Discuss with female patients of childbearing potential the need to use 2 different forms of contraception, including at least 1 primary form of contraception, simultaneously during LETAIRIS treatment and for 1 month following treatment discontinuation. If the patient has had a tubal sterilization or a Copper T 380A IUD or LNg 20 IUD inserted, no additional contraception is needed.
  - Primary forms of contraception include tubal sterilization, hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring), IUD, and a partner's vasectomy. A Copper T 380A IUD or LNg 20 IUD can be used alone (i.e., without a secondary form of contraception, as can tubal sterilization).
  - Secondary forms of contraception include barrier contraceptives such as latex condoms, diaphragms, and cervical caps.
- 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.

Risk of 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.

Hemoglobin must be measured prior to initiation of LETAIRIS and should be measured at 1 month and periodically thereafter. If a clinically significant decrease in hemoglobin is observed and other causes have been excluded, discontinuation of treatment should be considered.

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

*World Health Organization.

LETAIRIS Risk Information

Potential Risk of Reduced Male Fertility

The development of testicular tubular atrophy and impaired fertility has been linked to the chronic administration of ERAs in rodents. Patients should be informed of these findings. The impact on human testicular function and male fertility is not known.

Coadministration With Cyclosporine A

Use caution when LETAIRIS is coadministered with cyclosporine A because cyclosporine A may cause increased exposure to LETAIRIS.

Adverse Reactions

Placebo-adjusted adverse events in phase 3 clinical trials occurring in ≥2% of patients receiving LETAIRIS compared with patients receiving placebo were peripheral edema, nasal congestion, sinusitis, flushing, palpitations, nasopharyngitis, abdominal pain, and constipation. Most adverse drug reactions were mild to moderate and only nasal congestion was dose-dependent.

Peripheral edema was similar in younger patients (<65 years) receiving LETAIRIS (14%; 29/205) or placebo (13%; 13/104), and was greater in elderly patients (≥65 years) receiving LETAIRIS (29%; 16/56) compared to placebo (4%, 1/28).

Prescriber Responsibilities

Letairis™
ambrisentan
5 mg and 10 mg Tablets

- Read the LETAIRIS full prescribing information and understand the risks of LETAIRIS
- Complete the one-time LEAP Prescriber Enrollment and Agreement Form
- Use the patient Medication Guide and patient brochure to educate patients about the risks of LETAIRIS treatment
- Enroll all patients prescribed LETAIRIS in LEAP
- Order and review liver function tests (including aminotransferases and bilirubin) and pregnancy tests prior to initiating treatment with LETAIRIS and monthly during treatment
- Order and review hemoglobin concentrations and hematocrit prior to initiating treatment with LETAIRIS, at 1 month, and periodically thereafter
- Counsel patients who fail to comply with the program requirements and notify LEAP of any adverse events, including liver injury, or if any patient becomes pregnant during LETAIRIS treatment
- Re-enroll appropriate patients after the first 6 months and annually thereafter

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

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

Letairis™ ambrisentan
5 mg and 10 mg Tablets

INDICATION: LETAIRIS is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in patients with WHO Class II or III symptoms to improve exercise capacity and delay clinical worsening.

To enroll a patient in LEAP, please complete and fax this form to LEAP. FAX: 1-888-882-4035
Patient information will be forwarded to the specialty pharmacy you choose.

☐ Accredo ☐ Aetna ☐ Caremark ☐ CIGNA Tel-Drug ☐ CuraScript ☐ Fairview ☐ Walgreens Specialty Pharmacy (Medmark) ☐ WellPoint PrecisionRx

Patient Information (PLEASE PRINT)

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

SSN #: _____ Birthdate: _____ / _____ / _____ Gender: ☐ M ☐ F

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

Day Phone: (_____) _____ Evening Phone: (_____) _____

PLEASE FAX COPIES OF ALL RELATED PRIMARY AND SECONDARY INSURANCE INFORMATION TO THE FAX NUMBER ABOVE.

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 eligibility for benefits; (2) communicate with those covered by this authorization about my medical care; and (3) provide LETAIRIS™ (ambrisentan) support services, including facilitating the provision of LETAIRIS to me. I agree also that Gilead may contact me for reasons related to providing these services. I understand that once my health information has been disclosed to Gilead, federal privacy laws may no longer restrict its use or disclosure. 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. 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 cease using or disclosing my information for the purposes listed above, except as required by law or the LEAP program. I am entitled to a copy of this signed authorization, which expires 10 years from the date it is signed by me.

Patient/Guardian Signature: _____ Date: _____

By signing below, I acknowledge that I have read the patient Medication Guide and patient education brochure and that I have been informed about the risks of LETAIRIS, including the risks of liver injury, serious birth defects, low red blood cell count, and low sperm count. I acknowledge that I will be contacted by Gilead and/or its agents and contractors to receive counseling on the risks of LETAIRIS treatment, to ensure that I am completing the required liver function tests and pregnancy tests (for women who are able to become pregnant) and, if I am a woman who becomes pregnant, to obtain information about my pregnancy.

Patient/Guardian Signature: _____ Date: _____

Prescribing Physician Information (PLEASE PRINT)

Office Contact: _____

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

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

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

Prescription: LETAIRIS: ☐ 5 mg (30-day supply) ☐ 10 mg (30-day supply) Refills: _____

Instructions: _____

Ship to: Name: _____ Address: _____

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

☐ **Female patient of childbearing potential** ☐ **Negative pre-LETAIRIS pregnancy test**

☐ **Patient NOT of childbearing potential** ☐ **Pre-LETAIRIS liver function tests completed**

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

Diagnosis: ☐ Primary Pulmonary Hypertension (ICD 416.0) ☐ Pulmonary Hypertension, Secondary (ICD 416.8)

Related to: ☐ Congenital Heart Defects (ICD 745.____) ☐ Portal Hypertension (ICD 572.3) ☐ Drugs/Toxins (ICD _____)
☐ HIV (ICD 042____) ☐ Scleroderma (ICD 710.1) ☐ Lupus (ICD 710.0) ☐ Other: _____ (ICD _____)

I certify that I am prescribing LETAIRIS for a medically appropriate use in the treatment of pulmonary arterial hypertension, as described in the LETAIRIS full prescribing information. I have reviewed the Medication Guide and patient education brochure with the patient and have counseled them on the risks of LETAIRIS, including hepatotoxicity, teratogenicity, decreases in hemoglobin concentration and hematocrit, and the potential risk of reduced male fertility. I commit to ordering and reviewing liver function, pregnancy (if this patient is a female of childbearing potential), and hemoglobin tests in accordance with the LETAIRIS full prescribing information.

Prescribing Physician Signature: _____ Date: _____

Please visit www.letairis.com or www.gilead.com or call 1-866-664-LEAP (5327) for more information.
Please see accompanying patient Medication Guide and full prescribing information, including **boxed WARNING**.

GILEAD

WARNING: POTENTIAL LIVER INJURY

LETAIRIS (ambrisentan) can cause elevation of liver aminotransferases (ALT and AST) to at least 3 times the upper limit of normal (ULN). LETAIRIS treatment was associated with aminotransferase elevations >3x ULN in 0.8% of patients in 12-week trials and 2.8% of patients including long-term open-label trials out to one year. One case of aminotransferase elevations >3x ULN has been accompanied by bilirubin elevations >2x ULN. Because these changes are a marker for potentially serious liver injury, serum aminotransferase levels (and bilirubin if aminotransferase levels are elevated) must be measured prior to initiation of treatment and then monthly.

In the post-marketing period with another endothelin receptor antagonist (ERA), bosentan, rare cases of unexplained hepatic cirrhosis were reported after prolonged (>12 months) therapy. In at least one case with bosentan, a late presentation (after >20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of the suspect drug. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment.

Elevations in aminotransferases require close attention. LETAIRIS should generally be avoided in patients with elevated aminotransferases (>3x ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin >2x ULN, treatment should be stopped. There is no experience with the re-introduction of LETAIRIS in these circumstances.

CONTRAINDICATION: PREGNANCY

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 (4.1)]*. Pregnancy must therefore be excluded before the initiation of treatment with LETAIRIS and prevented thereafter by the use of at least two reliable methods of contraception unless the patient has had a tubal sterilization or Copper T 380A IUD or LNg 20 IUD inserted, in which case no other contraception is needed. Obtain monthly pregnancy tests.

Because of the risks of liver injury and birth defects, LETAIRIS is available only through a special restricted distribution program called the LETAIRIS Education and Access Program (LEAP), by calling 1-866-664-LEAP (5327). Only prescribers and pharmacies registered with LEAP may prescribe and distribute LETAIRIS. In addition, LETAIRIS may be dispensed only to patients who are enrolled in and meet all conditions of LEAP *[see WARNINGS, Prescribing and Distribution Program for LETAIRIS]*.

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

Please visit www.letairis.com or www.gilead.com for more information.

If you have questions or concerns, talk to your doctor.

GILEAD

Letairis™
ambrisentan
5 mg and 10 mg Tablets

LETAIRIS EDUCATION AND ACCESS PROGRAM (LEAP)

Patient Enrollment Guide

For starting therapy with LETAIRIS

INDICATION: LETAIRIS is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in patients with WHO Class II or III symptoms to improve exercise capacity and delay clinical worsening.

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

Letairis™
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5 mg and 10 mg Tablets

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

LEAP is a program to help you learn about the risks of LETAIRIS™ (ambrisentan), including the serious risks of liver injury and birth defects.

Your doctor enrolls you in LEAP. Once you are enrolled, you will get your LETAIRIS prescription through a specialty pharmacy that you and your doctor choose.

Why use a specialty pharmacy?

Specialty pharmacies provide products and services for patients with certain diseases. Only specialty pharmacies carry LETAIRIS. You and your doctor will choose the specialty pharmacy. LEAP makes sure the specialty pharmacy you choose is covered by your insurance. Your insurance company may require you to use a particular specialty pharmacy.

Your specialty pharmacy can help:

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

Participating specialty pharmacies:

- Accredo
- Aetna
- Caremark
- CIGNA Tel-Drug
- CuraScript
- Fairview
- Walgreens Specialty Pharmacy (Medmark)
- WellPoint PrecisionRx

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 about the risks of LETAIRIS. Ask questions. Make sure you understand what you need to do.

You and your doctor choose a specialty pharmacy to supply LETAIRIS.

Your doctor fills out the enrollment form. After you read and sign it, your doctor sends it to LEAP.

LEAP helps ensure the specialty pharmacy you choose is the best option for you and then sends them your information.

Your specialty pharmacy ships LETAIRIS to you each month. Before each shipment, you will be called to make sure that you have completed the tests you need and to review important information about LETAIRIS and LEAP.

What do I need to do for LEAP?

LETAIRIS can cause liver injury and serious birth defects if taken during pregnancy. Therefore, women must not be pregnant when they start LETAIRIS or during treatment.

Before you start LETAIRIS you must:

- Have a blood test to check your liver and red blood cells.
- Have a negative pregnancy test (for women who are able to get pregnant). Your doctor will decide when to do the test, depending on your menstrual cycle.

While you are taking LETAIRIS you must:

- Have monthly blood tests to check your liver.
- For women who are able to get pregnant you must also:
  - Have monthly pregnancy tests. Your doctor orders the tests.
  - Use 2 different forms of contraception, including at least 1 primary form of contraception, at the same time during LETAIRIS treatment and for 1 month following LETAIRIS discontinuation, unless you have had a tubal sterilization or a Copper T 380A IUD or LNg 20 IUD inserted, in which case no other contraception is needed. Talk with your doctor or gynecologist (a doctor who specializes in female reproduction) about the forms of birth control that are suitable for you.

You must complete all of the tests your doctor orders.

WARNING: POTENTIAL LIVER INJURY

LETAIRIS (ambrisentan) can cause elevation of liver aminotransferases (ALT and AST) to at least 3 times the upper limit of normal (ULN). LETAIRIS treatment was associated with aminotransferase elevations >3x ULN in 0.8% of patients in 12-week trials and 2.8% of patients including long-term open-label trials out to one year. One case of aminotransferase elevations >3x ULN has been accompanied by bilirubin elevations >2x ULN. Because these changes are a marker for potentially serious liver injury, serum aminotransferase levels (and bilirubin if aminotransferase levels are elevated) must be measured prior to initiation of treatment and then monthly.

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Because of the risks of liver injury and birth defects, LETAIRIS is available only through a special restricted distribution program called the LETAIRIS Education and Access Program (LEAP), by calling 1-866-664-LEAP (5327). Only prescribers and pharmacies registered with LEAP may prescribe and distribute LETAIRIS. In addition, LETAIRIS may be dispensed only to patients who are enrolled in and meet all conditions of LEAP *[see WARNINGS, Prescribing and Distribution Program for LETAIRIS]*.

Please visit www.letairis.com or www.gilead.com for more information.

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

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Letairis™
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LETAIRIS Therapy

What you need to know

INDICATION: LETAIRIS is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in patients with WHO Class II or III symptoms to improve exercise capacity and delay clinical worsening.

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

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What do I need to do to get started?

1. **You and your doctor will review the patient Medication Guide and patient education brochure to help you learn about the risks of LETAIRIS™ (ambrisentan), including the serious risks of liver injury and birth defects.**

2. **To start treatment with LETAIRIS, your doctor must enroll you in the LETAIRIS Education and Access Program (LEAP). If you are not already enrolled in LEAP, ask your doctor for more information.**

   LEAP is a program to help you learn about the risks of LETAIRIS including the serious risks of liver injury and birth defects.

3. **Once you are enrolled in LEAP, you will get your LETAIRIS prescription through a specialty pharmacy. Only specialty pharmacies carry LETAIRIS.**

4. **The specialty pharmacy ships LETAIRIS to you each month. Before each shipment, you will be called to make sure you have completed the tests you need and to review important information about LETAIRIS and LEAP.**

LETAIRIS™ (le-TAIR-is) Tablets (ambrisentan)

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?

- **Possible liver injury.**

  LETAIRIS can cause liver injury. You must have a blood test to check your liver function before you start LETAIRIS and each month after that. Your doctor will order these blood tests. (See "What are the possible side effects of LETAIRIS?" for information about the signs of liver problems.) **Tell your doctor if you have had moderate or severe liver problems, including liver problems while taking other medicines.**

- **Serious birth defects.**

  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 different reliable forms of birth control at the same time, during LETAIRIS treatment and for one month after stopping LETAIRIS. 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. 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.

Letairis™
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5 mg and 10 mg Tablets

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.
- **your blood tests show possible liver injury.**

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.

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.
- During treatment your doctor will test your blood for signs of side effects to your liver and red blood cells.

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:

- **Possible liver injury.** (See "What is the most important information I should know about LETAIRIS?") Call your doctor right away if you have any of these symptoms of liver problems: loss of appetite, nausea, vomiting, fever, unusual tiredness, right upper stomach pain, yellowing of the skin or the whites of your eyes (jaundice), dark urine, or itching.
- **Serious birth defects.** (See "What is the most important information I should know about LETAIRIS?")
- **Low sperm count.** LETAIRIS can lower sperm count in animals. If this happens in men, they may lose the ability to father children. Talk with your doctor if you have any questions or concerns.

The most common side effects of LETAIRIS are:

- Lowering of red blood cell count
- Swelling of legs and ankles (edema)
- Stuffy nose (nasal congestion)
- Inflamed nasal passages (sinusitis)
- Hot flashes or getting red in the face (flushing)
- Feeling your heart beat (palpitations)
- Red and sore throat and nose
- Stomach pain
- Constipation
- Shortness of breath
- Headache

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How should I store LETAIRIS?

Store LETAIRIS at less than 86°F (30°C), in the package it comes in.

General information about LETAIRIS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any concerns or questions about LETAIRIS, ask your doctor or other healthcare provider. This Medication Guide is only a summary of some important information about LETAIRIS. Your doctor can give you information about LETAIRIS that was written for healthcare professionals. Do not use LETAIRIS for any condition other than that for which it was prescribed. Do not share LETAIRIS with other people. It may harm them.

Call 1-866-664-LEAP (5327) or visit www.letairis.com or www.gilead.com for more information.

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.

Questions to ask your doctor

"What can I expect from LETAIRIS treatment?"

"What are the risks and side effects I should know about?"

"What special instructions are there for taking LETAIRIS?"

"Are there any medicines I cannot take while taking LETAIRIS?"

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

/s/

Robert Temple

6/15/2007 04:56:32 PM