DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022081/S-019

SUPPLEMENT APPROVAL

Gilead
Attention: Saima Malik, M.Sc.
Senior Associate, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Malik:

Please refer to your Supplemental New Drug Application (sNDA) dated November 22, 2011, received November 23, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Letairis (ambrisentan) 5 mg and 10 mg Tablets.

We acknowledge receipt of your amendments dated February 24, March 14, April 17 and 19, August 21, and November 21, 2012, and your risk evaluation and mitigation strategy (REMS) assessment dated August 9, 2012.

The August 21, 2012, submission constituted a complete response to our June 7, 2012, action letter.

This "Prior Approval" supplemental new drug application provides for a proposed modification to the approved REMS, and labeling revised as follows (additions are shown as underlined text and deletions are shown as ~~strikethrough~~ text):

1. In **HIGHLIGHTS** and **FULL PRESCRIBING INFORMATION**, the text in the Boxed Warning was revised as follows:

> **WARNING: ~~CONTRAINDICATED IN PREGNANCY~~EMBRYO-FETAL TOXICITY**
>
> Do not administer ~~LETAIRIS~~Letairis to a pregnant ~~woman~~female because it may cause fetal harm. ~~LETAIRIS~~Letairis is very likely to produce serious birth defects if used by pregnant ~~women~~females, as this effect has been seen consistently when it is administered to animals [see Contraindications (4.1), Use in Specific Populations (8.1)].
>
> ~~Pregnancy must therefore be excluded~~Exclude pregnancy before the initiation of treatment with ~~LETAIRIS and prevented during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS, in which case no additional contraception is needed.~~ Letairis. Females of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for one month after treatment. Obtain monthly pregnancy tests ~~*[see*~~

~~*Warnings and Precautions (5.1)]*~~. during treatment and 1 month after discontinuation of treatment *[see Use in Specific Populations (8.6)]*.

Because of the risk of ~~birth defects, LETAIRIS is available~~embryo-fetal toxicity, females can only receive Letairis through a restricted program ~~under a Risk Evaluation and Mitigation Strategy (REMS) called the LETAIRIS Education and Access Program (LEAP). As a component of the LETAIRIS REMS, prescribers, patients, and pharmacies must enroll in the~~called the Letairis REMS program *[see Warnings and Precautions (~~5.1~~5.2)]*.

2. In **HIGHLIGHTS/RECENT MAJOR CHANGES**, the following text was added:

Boxed Warning	08/2013
Dosage and Administration (2.2)	08/2013
Warnings and Precautions, Embryo-fetal Toxicity (5.1)	08/2013
Warnings and Precautions, Letairis REMS Program (5.2)	08/2013

3. Under **DOSAGE AND ADMINISTRATION**, the following text was added/deleted:

~~Healthcare professionals who prescribe LETAIRIS must enroll in the restricted program called LEAP and must comply with the required monitoring to ensure safe use of LETAIRIS *[see Warnings and Precautions (5.1)].*~~

2.2 Women of Childbearing~~Pregnancy Testing in Females of Reproductive~~ Potential

Initiate treatment with ~~LETAIRIS~~ Letairis in ~~women~~ females of ~~childbearing~~ reproductive potential only after a negative pregnancy test ~~*[see Contraindications (4.1) and Warnings and Precautions (5.1*~~. Obtain monthly pregnancy tests during treatment *[see Use in Specific Populations (8.6)]*.

4. Under **CONTRAINDICATIONS/Pregnancy**, the following text was added/deleted:

~~LETAIRIS~~Letairis may cause fetal harm when administered to a pregnant ~~woman. Ambrisentan was teratogenic at oral doses of ≥15 mg/kg/day in rats and ≥7 mg/kg/day in rabbits; it was not studied at lower doses. In both species, there were abnormalities of the lower jaw and hard and soft palate, malformation of the heart and great vessels, and failure of formation of the thymus and thyroid. Teratogenicity is a class effect of endothelin receptor antagonists. There are no data on the use of LETAIRIS in pregnant women.LETAIRIS is contraindicated in women~~female. Letairis is contraindicated in females who are ~~or may become~~ pregnant. Letairis was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus~~. Pregnancy must be excluded before the initiation of treatment with LETAIRIS and prevented during treatment and for one month after stopping treatment *[see Dosage and Administration (2.2), Warnings and Precautions (5.1 [see Warnings and Precautions (5.1, 5.2) and Use in Specific Populations (8.1)]*.

5. Under **WARNINGS AND PRECAUTIONS**, the following text was added/deleted:

~~5.1 LETAIRIS Education and Access Program (LEAP)~~ 5.1 Embryo-fetal Toxicity

Letairis may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods and obtain monthly pregnancy tests *[see Dosage and Administration (2.2), and Use in Specific Populations (8.1, 8.6)]*.

Letairis is only available for females through a restricted program under a REMS *[see Warnings and Precautions (5.2)]*.

5.2 Letairis REMS Program

~~Because of the risk of birth defects, LETAIRIS~~For all females, Letairis is available only through a restricted program called the ~~LETAIRIS Education and Access Program (LEAP).~~ Letairis REMS, because of the risk of embryo-fetal toxicity *[*see *Contraindications (4.1), Warnings and Precautions (5.1), and Use in Specific Populations (8.1, 8.6)]*.
~~Required components of LEAP:~~
Notable requirements of the Letairis REMS program include the following:

Prescribers must be certified with the program by enrolling and completing training.

~~Healthcare professionals who prescribe LETAIRIS must complete the LEAP Prescriber Enrollment and Agreement Form, enroll in the program, and comply with the REMS requirements.~~All females, regardless of reproductive potential, must enroll in the Letairis REMS program prior to initiating Letairis. Male patients are not enrolled in the REMS.

~~To receive LETAIRIS, all patients must complete a patient enrollment form and be re-enrolled annually by their prescriber. For women of childbearing potential, (1) a pregnancy test must be ordered and reviewed by the prescriber prior to initiation of LETAIRIS treatment and monthly during treatment, (2) she must agree to be contacted prior to each shipment to confirm that a pregnancy test was completed, (3) she must agree to be counseled on the requirements of the REMS program and the risks of LETAIRIS, and (4) she must agree to be contacted by Gilead if she becomes pregnant while on LETAIRIS or within 30 days of treatment discontinuation.~~Females of reproductive potential must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.6)]*.

Pharmacies that dispense ~~LETAIRIS~~Letairis must ~~enroll in~~be certified with the program and ~~agree to comply with the REMS requirements~~must dispense to female patients who are authorized to receive Letairis.

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

~~5.4~~5.5 Decreased Sperm Counts

~~In a 6-month study of another endothelin receptor antagonist, bosentan, 25 male patients with WHO functional class III and IV PAH and normal baseline sperm count were evaluated for effects on testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with bosentan. One patient developed marked oligospermia at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Bosentan was discontinued and after 2 months the sperm count had returned to baseline levels. In 22 patients who completed 6 months of treatment, sperm count remained within the normal range and no changes in sperm morphology, sperm motility, or hormone levels were observed. Based on these findings and preclinical data *[see Nonclinical Toxicology (13.1)]* from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as LETAIRIS have an adverse effect on spermatogenesis.~~

Decreased sperm counts have been observed in human and animal studies with another endothelin receptor antagonist and in animal fertility studies with ambrisentan. Letairis may have an adverse effect on spermatogenesis. Counsel patients about potential effects on fertility *[see Special Populations (8.6) and Nonclinical Toxicology (13.1)].*

6. Under **ADVERSE REACTIONS**, the following text was added/deleted:

Clinically significant adverse reactions that appear in other sections of the labeling include:

Embryo-fetal toxicity *[see Warnings and Precautions (5.1), Use in Specific Populations (8.1)]*

Fluid Retention *[see Warnings and Precautions (5.3)]*

Pulmonary Edema with PVOD *[see Warnings and Precautions (5.4)]*

~~See~~Decreased Sperm Count *[see Warnings and Precautions (5.5)~~ ~~for discussion of hematological changes.]*

Hematologic changes *[see Warnings and Precautions (5.6)]*

7. Under **USE IN SPECIFIC POPULATIONS,** the following text was added/deleted:

8.1 Pregnancy

Pregnancy Category X ~~*[see Contraindications (4.1)]*~~. ~~Treat women of childbearing potential only after a negative pregnancy test and treat only women who are using acceptable methods of contraception. Pregnancy tests should be obtained monthly in women of childbearing potential taking LETAIRIS *[see Warnings and Precautions (5.1)]*.~~

~~**8.3 Nursing Mothers**~~

Risk Summary

Letairis may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Letairis was teratogenic in rats and rabbits at doses which resulted in exposures of 3.5 and 1.7 times respectively the human dose of 10 mg

per day. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus *[see Contraindications (4.1), Warnings and Precautions (5.1)]*.

Animal Data

Letairis was teratogenic at oral doses of ≥ 15 mg/kg/day (AUC 51.7 h•µg/ml) in rats and ≥ 7 mg/kg/day (24.7 h•µg/ml) in rabbits; it was not studied at lower doses. These doses are of 3.5 and 1.7 times respectively the human dose of 10 mg per day (14.8 h•µg/ml) based on AUC. In both species, there were abnormalities of the lower jaw and hard and soft palate, malformation of the heart and great vessels, and failure of formation of the thymus and thyroid.

~~It is not known whether ambrisentan is excreted in human milk. Breastfeeding while receiving LETAIRIS is not recommended.~~ A preclinical study in rats has shown decreased survival of newborn pups (mid and high doses) and effects on testicle size and fertility of pups (high dose) following maternal treatment with ambrisentan from late gestation through weaning. Doses tested were 17x, 51x, and 170x (~~low, mid, high dose, respectively~~on a mg/kg:mg/m2 basis) the maximum oral human dose of 10 mg ~~on a mg/mm^2 basis.~~and an average adult body weight of 70 kg.

8.3 Nursing Mothers

It is not known whether ambrisentan is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from Letairis, a decision should be made whether to discontinue nursing or discontinue Letairis, taking into account the importance of the drug to the mother.

8.6 Females and Males of Reproductive Potential

Pregnancy Testing

Female patients of reproductive potential must have a negative pregnancy test prior to initiation of treatment, monthly pregnancy test during treatment, and 1 month after stopping treatment with Letairis. Advise patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patient on the potential risk to the fetus and patient options *[see Boxed Warning and Dosage and Administration (2.2)]*.

Contraception

Female patients of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for 1 month after stopping treatment with Letairis. Patients may choose one highly effective form of contraception (intrauterine devices (IUD), contraceptive implants, or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling *[see Boxed Warning]*.

Infertility

Males

In a 6-month study of another endothelin receptor antagonist, bosentan, 25 male patients with WHO functional class III and IV PAH and normal baseline sperm count were evaluated for effects on testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with bosentan. One patient developed marked oligospermia at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Bosentan was discontinued and after 2 months the sperm count had returned to baseline levels. In 22 patients who completed 6 months of treatment, sperm count remained within the normal range and no changes in sperm morphology, sperm motility, or hormone levels were observed. Based on these findings and preclinical data *[see Nonclinical Toxicology (13.1)]* from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as Letairis have an adverse effect on spermatogenesis. Counsel patients about the potential effects on fertility *[see Warnings and Precautions (5.5)]*.

8. Under **HOW SUPPLIED/STORAGE AND HANDLING**, the following text was added/deleted:

~~LETAIRIS is available only through the LETAIRIS Education and Access Program (LEAP) by calling 1-866-664-LEAP (5327) or by logging on to www.letairis.com.~~
~~LETAIRIS~~Letairis film-coated, tablets are supplied as follows:

Tablet Strength	Package Configuration	NDC No.	Description of Tablet; Debossed on Tablet; Size
5 mg	30 count blister	61958-0801-2	Square convex; pale pink; "5" on side 1 and "GSI" on side 2; 6.6 mm Square
	30 count bottle	61958-0801-1	
	10 count blister	61958-0801-3	
	10 count bottle	61958-0801-5	
10 mg	30 count blister	61958-0802-2	Oval convex; deep pink; "10" on side 1 and "GSI" on side 2; 9.8 mm x 4.9 mm Oval
	30 count bottle	61958-0802-1	
	10 count blister	61958-0802-3	
	10 count bottle	61958-0802-5	

9. Under **PATIENT COUNSELING INFORMATION**, the following text was added/deleted:

~~**17.1 LETAIRIS Education and Access Program (LEAP)**~~
17.1 Embryo-fetal toxicity
Instruct patients on the risk of fetal harm when Letairis is used in pregnancy *[see Warnings and Precautions (5.1) and Use in Special Populations (8)]*. Female patients

must enroll in the Letairis REMS program. Instruct females of reproductive potential to immediately contact their physician if they suspect they may be pregnant.

17.2 Letairis REMS Program

~~Advise the patient that LETAIRIS~~For female patients, Letairis is only available ~~only~~ through a restricted program called ~~LEAP.As a component of LEAP, prescribers must review the contents of the LETAIRIS Medication Guide and the LETAIRIS Patient Enrollment Guide before initiating treatment with LETAIRIS~~the Letairis REMS *[see Contraindications (4.1), Warnings and Precautions (5.2)]*. Male patients are not enrolled in the Letairis REMS.

Inform ~~the patient that LETAIRIS is available only from Certified Specialty Pharmacies enrolled in LEAP. Provide patients with a list of Certified Specialty Pharmacies.~~
~~As a component of LEAP, Certified Specialty Pharmacies must provide a copy of the Medication Guide to patients or caregivers each time LETAIRIS is dispensed. Patients must be instructed to read the Medication Guide each time they receive LETAIRIS because new information may be available. In addition, Certified Specialty Pharmacies must contact patients before each shipment to confirm that the patient will be available to receive the LETAIRIS shipment, and, in the case of women of childbearing potential, to confirm that a pregnancy test has been completed.~~
~~Patients must complete a patient enrollment form and be re-enrolled annually by their prescribers using the LEAP Patient Enrollment and Consent form to confirm that they understand the risks of LETAIRIS.~~
~~Patients may be asked to participate in a survey to evaluate the effectiveness of LEAP.~~

~~**17.2 Pregnancy**~~

~~Instruct patients that the risks associated with LETAIRIS include serious birth defects if used by pregnant women:~~

- ~~Educate and counsel women of childbearing potential to use highly reliable contraception during LETAIRIS treatment and for one month after stopping treatment. If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS for pregnancy prevention, no additional contraception is needed. Women who do not choose one of these methods should always use two acceptable forms of contraception: one hormone method and one barrier method, or two barrier methods where one method is the male condom.~~
- ~~Acceptable hormone methods include: progesterone injectables, progesterone implants, combination oral contraceptives, transdermal patch, and vaginal ring.~~female patients (and their guardians, if applicable) of the following notable requirements:

- ~~Acceptable barrier methods include: diaphragm (with spermicide), cervical cap (with spermicide), and the male condom.~~All female patients must sign an enrollment form.

- ~~Partner's vasectomy must be used along with a hormone method or a barrier method.~~Advise female patients of reproductive potential that they must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.6)]*.

- Educate and counsel ~~women~~females of ~~childbearing~~reproductive potential on the use of emergency contraception in the event of unprotected sex or known or suspected contraceptive failure ~~*[see Boxed Warning, Contraindications (4)]*~~.

~~Instruct patient to immediately contact their physician if they suspect they may be pregnant.~~

- Advise pre-pubertal females to report any changes in their reproductive status immediately to their prescriber.

Review the Letairis Medication Guide and REMS educational material with female patients.

A limited number of pharmacies are certified to dispense Letairis. Therefore, provide patients with the telephone number and website for information on how to obtain the product.

10. There are several editorial changes noted throughout the label,(i.e. LETAIRIS was changed to Letairis; the sections were re-numbered; the Table of Contents was updated to reflect the additional sections and re-numbering).

11. The revision date and version number were updated.

The following changes were made to the Medication Guide:

1. Under **What is the most important information I should know about Letairis?**, the following text was added:

- **~~Women~~Females must not be pregnant when they start taking ~~LETAIRIS~~Letairis or become pregnant during treatment with Letairis.**

- ~~Women~~Females who are able to get pregnant must have a negative pregnancy test before beginning treatment with ~~LETAIRIS~~Letairis and each month during treatment~~.~~ with Letairis. Talk to your doctor about your menstrual cycle. Your doctor will decide when to do the ~~test,~~tests, and order the tests for you depending on your menstrual cycle.

  - Females who are able to get pregnant are women who:

    - Have entered puberty, even if they have not started their period, **and**

    - Have a uterus, **and**

    - Have not gone through menopause (have not had a period for at least 12 months for natural reasons, or who have had their ovaries removed)

  - Females who are not able to get pregnant are females who:

    - Have not yet entered puberty, **or**

    - Do not have a uterus, **or**

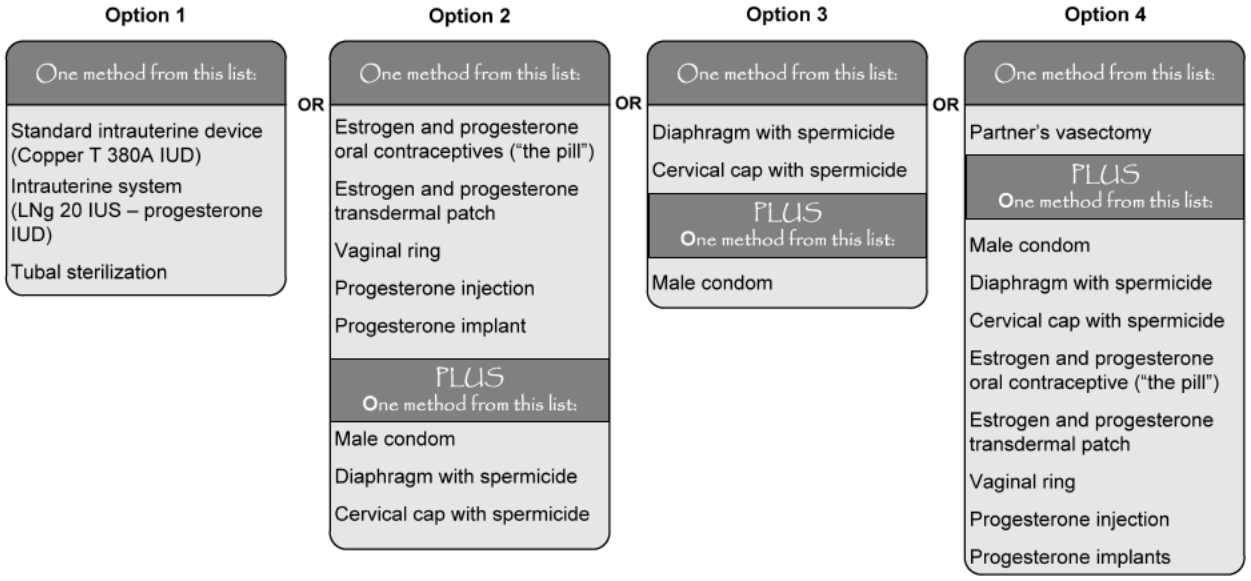
- Have gone through menopause (have not had a period for at least 12 months for natural reasons, or who have had their ovaries removed)

~~Women~~Females who are able to get pregnant must use two acceptable forms of birth control, during ~~LETAIRIS~~ treatment with Letairis, and for one month after stopping ~~LETAIRIS~~Letairis because the medicine may still be in the body.

- If you have had a tubal sterilization or have an IUD (intrauterine device), these methods can be used alone and no other form of birth control is needed.
- Talk with your doctor or gynecologist (a doctor who specializes in female reproduction) to find out about ~~how~~options for acceptable forms of birth control that you may use to prevent pregnancy during treatment with Letairis.
- If you decide that you want to change the form of birth control that you use, talk with your doctor or gynecologist to be sure that you choose another acceptable form of birth control.

See the chart below for Acceptable Birth Control Options during treatment with Letairis.

Acceptable Birth Control Options



If you are the parent or caregiver of a female child who started taking Letairis before reaching puberty, you should check your child regularly to see if she is developing signs of puberty. Tell your doctor right away if you notice that she is developing breast buds or any pubic hair. Your doctor should decide if your child has reached puberty. **Your child may reach puberty before having her first menstrual period.**

~~LETAIRIS is available~~Females can only receive Letairis through a restricted program called the ~~LETAIRIS Education and Access Program (LEAP). To receive LETAIRIS~~Letairis Risk Evaluation and Mitigation Strategy (REMS) program. If you are a female who can get pregnant, you must talk to your doctor, understand the benefits and risks of ~~LETAIRIS~~Letairis, and agree to all of the instructions in the ~~LEAP~~Letairis REMS program.

Males can receive Letairis without taking part in the Letairis REMS program.

2. Under **What is ~~LETAIRIS~~Letairis?**, the following text was added:
   - ~~LETAIRIS~~Letairis is a prescription medicine to treat pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of your lungs.
   - ~~LETAIRIS~~Letairis can improve your ability to exercise and it can help slow down the worsening of your physical condition and symptoms.
   - It is not known if Letairis is safe and effective in children.

3. Under **Who should not take ~~LETAIRIS~~Letairis?**, the following text was added/deleted:

Do not take ~~LETAIRIS~~Letairis if:

- you are pregnant, plan to become pregnant, or become pregnant during treatment with **~~LETAIRIS~~Letairis**. **~~LETAIRIS~~Letairis** can cause serious birth defects. (See the Medication Guide section above called "What is the most important information I should know about ~~LETAIRIS~~Letairis?") Serious birth defects from ~~LETAIRIS~~Letairis happen early in pregnancy.
- ~~LETAIRIS has not been studied in children.~~

4. Under **What should I avoid while taking ~~LETAIRIS~~Letairis?**, the following text was added/deleted:

- **Do not get pregnant** while taking ~~LETAIRIS~~Letairis. (See the serious birth defects section of the Medication Guide above called "What is the most important information I should know about ~~LETAIRIS~~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~~
- **It is not known if Letairis passes into your breast milk. You should not breastfeed** if you are taking Letairis. Talk to your doctor about the best way to feed your baby if you take Letairis.

5. Under **What are the possible side effects of ~~LETAIRIS~~Letairis?,** the following text was added/deleted:

~~Serious~~Letairis can cause serious side effects ~~of LETAIRIS include~~including:

6. Under **How should I store Letairis?**, the following text was added/deleted:

Store ~~LETAIRIS~~Letairis at room temperature between 68 °F to 77 °F (20 °C to 25 °C), in the package it comes in.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text. In addition, we found the REMS assessment to be adequate.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Letairis was originally approved on May 29, 2009, and REMS modifications were approved on July 1 and August 5, 2009, August 24 and October 13, 2010, and March 3, 2011, and February 15, 2012, and last modified on October 19, 2012. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of the above revisions to the Medication Guide and revisions to relevant sections of the appended REMS materials to conform the content to the above referenced labeling changes. The REMS was further revised to eliminate enrollment of males in the REMS program, and to revise the requirements applicable to females (females of reproductive potential and females of non-reproductive potential).

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application

under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed modified REMS, submitted on August 9, 2012, and appended to this letter, is approved.

The REMS Assessment Plan should include but is not limited to the following data:

1. Assessment of the dispensing of the *Medication Guide* in accordance with 21 CFR 208.24

2. Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

3. An evaluation of patients' awareness and understanding of teratogenicity associated with Letairis, including an evaluation of patient-reported compliance with contraceptive use and monthly pregnancy testing for FRP

4. An evaluation of healthcare providers' awareness and understanding of:

    a. The risk of teratogenicity associated with Letairis
    b. The need to exclude a pregnancy before initiating Letairis therapy
    c. The need for patients to consistently use effective birth control and what the effective methods of contraception are
    d. The need to promptly discontinue Letairis therapy in the event of a pregnancy

5. Number of dispensers and prescribers (stratified by medical specialty) certified, and patients enrolled during the current REMS assessment reporting period and during each previous REMS assessment reporting period

6. Patient demographics for the current REMS assessment reporting period and for previous REMS assessment reporting periods to include gender, age, diagnosis, and number (%) of FRP

7. The number of patients who experience a shipment delay due to reporting a missed pregnancy test, the reasons for the missed pregnancy test, and any adverse events occurring as a result of treatment interruptions

8. The frequency and reasons for dispensing >30 day supply to FRP

9. Report on *Reproductive Potential Status Forms* including:

    a. Number of Reproductive Potential Status forms received
    b. Number of status changes to a FRP, including rationale for the change as indicated on the form and time between receipt of form and start of routine monthly pregnancy testing
    c. Number of status changes to a FNRP, including rationale for the change as indicated on the form

10. A summary of audit activities for the REMS Coordinating Center and certified pharmacies, reports of critical observations identified and the associated corrective and preventive action (CAPA) plans, and whether the CAPA plans were satisfactorily completed

11. An analysis of the post-marketing cases of pregnancy reported in association with Letairis (during the reporting period and cumulative) with attention to but not limited to:

    a. The number of pregnancy exposures* reported (during the reporting period and cumulative) and stratified by source (spontaneous report, reported via the Letairis REMS Coordinating Center, enrolled in the pregnancy registry), age, and other demographics.

    b. The pregnancy outcome for each exposed pregnancy reported (during the reporting period and cumulative).

    c. Follow-up of outstanding pregnancy reports from previous assessment reporting period;

    d. Root cause analysis of each reported pregnancy to determine the reason the Letairis REMS program failed to prevent the pregnancy exposure; and

    e. Discussion of any new information provided in the most recent Periodic Safety Update Report (PSUR) or Periodic Benefit Risk Evaluation Report (PBRER) regarding pregnancy. In the electronic REMS assessment submission, include a hyperlink to the most recent PSUR/PBRER that provides information on worldwide pregnancies.

    * All pregnancy exposures reported to the sponsors from any source should be reported and analyzed as part of the REMS assessment. Pregnancy exposures will be recorded within the Letairis REMS database as well as the global safety database, with appropriate linkage to allow matching of the cases reported in the Letairis REMS database to cases in the global safety database.

12. With respect to Letairis REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goal or whether the goal or such elements should be modified

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022081# REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.
Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 022081 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022081
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022081
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

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

If you have any questions, please call:

Lori Anne Wachter, RN, BSN, RAC
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
REMS

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

/s/

MARY R SOUTHWORTH
08/17/2013