DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022081/S-040

SUPPLEMENT APPROVAL

Gilead Sciences, Inc.
Attention: April Given
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Given:

Please refer to your Supplemental New Drug Application (sNDA) dated May 31, 2018, received June 1, 2018, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Letairis (ambrisentan) 5 mg and 10 mg Tablets.

This supplemental new drug application provides for revisions to the approved labeling for conversion to comply with the Pregnancy and Lactation Rule (PLLR), and proposed modifications to the approved Letairis risk evaluation and mitigation strategy (REMS).

APPROVAL & LABELING

We have completed our review of this supplemental application and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

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 Prescribing Information, and 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 include 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 Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), 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 (REMS) REQUIREMENTS

The REMS for Letairis was originally approved on October 29, 2009, and the most recent REMS modification was approved on September 27, 2017. 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 modification to the REMS consists of an update to the Prescriber Guide to conform with the PLLR conversion and incorporate content for females who cannot get pregnant, modifications to the Guide for Females Who Can Get Pregnant to incorporate information on females who cannot get pregnant and retitle it as Guide for Female Patients, as well as corresponding updates to the REMS document, Patient Enrollment and Consent Form, Prescriber Enrollment and Agreement Form, and website screenshots.

Additionally, in accordance with section 505-1 of the FDCA, we have determined that the following REMS modification is necessary to minimize burden on the healthcare delivery system of complying with the REMS:

Medication Guide: We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Letairis outweigh its risks. The Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Your proposed modified REMS, submitted on June 1, 2018, amended and appended to this letter, is approved. The modified REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on August 7, 2013.

The revised REMS assessment plan must include but is not limited to the following items.

1. Enrollment into the Letairis REMS Program

    a) Patients: new and total across previous assessment reporting periods who received at least one shipment of Letairis, age, gender, diagnosis, number and percentage of females of reproductive potential, number and percentage of pre-pubertal females

    b) Dispensers: new and total

    c) Prescribers: new and total, stratified by medical specialty

2. Report on Letairis REMS *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification* forms including:

    a. Number of *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification* forms received

        i. Number of *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification* forms returned reporting annual verification that a patient remains a Pre-Pubertal Female

        ii. Number of *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification* forms returned reporting annual verification that a patient remains a Pre-Pubertal Female expected

        iii. Whether any shipments were suspended as a result of the prescriber's failure to return the form for pre-pubertal females

    b. Number of status changes to a female of reproductive potential, including

        i. rationale for the change as indicated on the form and time between receipt of form and start of routine pregnancy testing

        ii. number of times Letairis was dispensed prior to the patient getting their first pregnancy test following the status change, any resulting adverse events, and corrective actions

    c. Number of status changes to a female of non-reproductive potential, including rationale for the change as indicated on the form

3. Compliance with the Letairis REMS

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

b. 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 event occurring as a result of treatment interruptions

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

4. 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

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.

5. 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

-We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.
e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

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 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.

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.

Prominently identify any 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

or

NEW SUPPLEMENT FOR NDA 022081/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022081/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022081/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022081/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 022081

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY R SOUTHWORTH
11/30/2018